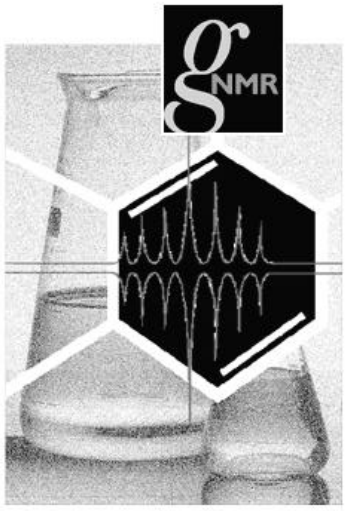
Simulation of one-dimensional NMR spectra

a companion to the gNMR User Manual



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This booklet is a companion to the manual of the gNMR package for NMR simulation. It provides general background about the use of simulation for spectrum analysis.

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1. The role of simulation in spectrum analysis

1.1. Introduction

NMR spectra are usually recorded in order to analyze a sample. The desired analysis can be quite simple: if you have a mixture of two compounds, each having a single NMR resonance, integration of the area of the two peaks can be used to determine the relative concentrations. Usually, NMR spectra are more complicated than this, and the analysis can become correspondingly more difficult. In such cases, simulation can often be very helpful.

Simulation in the strict sense is the calculation of an NMR spectrum from a set of parameters (shifts, coupling constants).

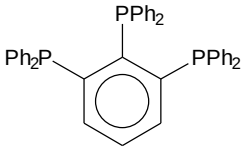
> The term simulation is also used frequently to denote the calculation of a spectrum from a molecular structure, which involves prediction of the parameters from the structure as an intermediate step.

In some cases ("first-order spectra") a few simple rules suffice to predict the appearance of an NMR-spectrum, and simulation is not necessary. There are many cases, however, where these rules do not hold ("second-order spectra") and then computer simulation is the only practical way to predict the appearance of a spectrum from its basic parameters.

Let us walk through a few examples where simulation might play a role in the analysis. These examples illustrate different questions one can have about a spectrum, and therefore different applications of simulation. Sometimes, you just want to know whether a spectrum can belong to a certain compound (#1,3). Sometimes, you are interested in the numerical values of parameters, because they can tell you something about the structure of a compound (#2). And sometimes, simulation may even be used to extract some mechanistic information from a spectrum (#4).

Example 1. Synthesis of a new triphosphine

An attempt to prepare compound ***1*** produced a white solid with the $^{31}P\{^{1}H\}$ NMR spectrum shown in Figure 1. Could this really be the desired product? If so, what are the shifts and coupling constant (needed for publication)?



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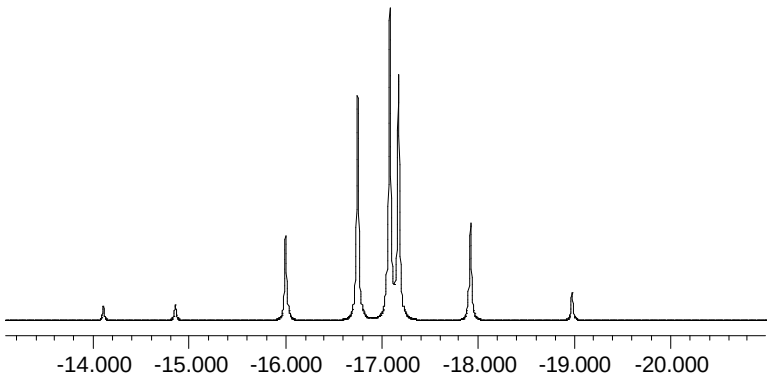
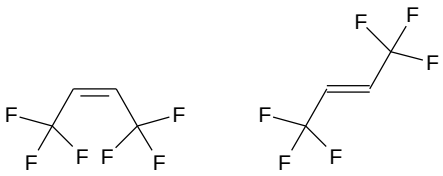


*Figure 1. $^{31}P\{^{1}H\}$ NMR spectrum (80.96 MHz; ^{1}H = 200 MHz) of phosphine **1**?*

Simulation quickly shows that this spectrum can indeed be explained completely by a strongly coupled A_2B system with $?_A$ = -17.5 ppm, $?_B$ = -16 ppm, and J_{AB} = 120 Hz. Without simulation, you might have thought that you had a mixture of several compounds. Note that there are *no* peaks in this spectrum with a separation of 120 Hz!

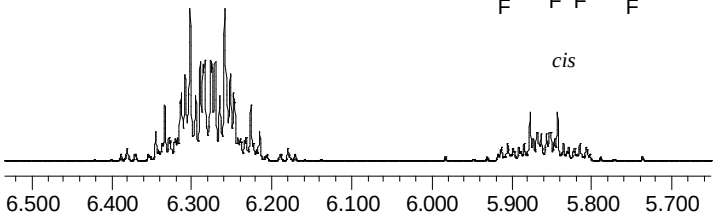
Example 2. *cis* and/or *trans* isomers?

An attempt to prepare 1,1,1,4,4,4-hexafluoro-2-butene gave a product with the ^{1}H NMR spectrum shown in Figure 2. Did the synthesis succeed? And if so, is the product the *cis*-isomer, the *trans*-isomer or a mixture?



cis *trans*

Figure 2. ^{1}H spectrum of mixture of cis and trans hexafluorobutenes?



Both isomers are $AA'X_3X'_3$ systems, which always give rise to symmetrical spectra. Since the spectrum contains two symmetrical multiplets, it seems likely that it is a mixture of the two isomers. But which is which? Even though the multiplets look complicated, their appearance is governed by only four coupling constants: $^{2}J_{HH}$, $^{3}J_{HF}$, $^{4}J_{HF}$ and $^{5}J_{FF}$. A bit of trial-and-error simulation, followed by iterative optimization, will yield values for all four parameters. The most important one is probably J_{HH}, which turns out to be *ca* 11 Hz for the low-field multiplet, and *ca* 15.5 Hz for the high-field multiplet. This is a strong indication that the major component is the *cis* isomer.

Example 3. An unknown rhodium complex.

Reaction of diphosphine ligand ***2*** with a rhodium complex resulted in a compound with the $^{31}P\{^{1}H\}$ NMR spectrum shown in Figure 3. Is it possible to deduce anything about the stoichiometry and structure of the complex?

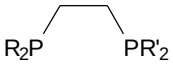


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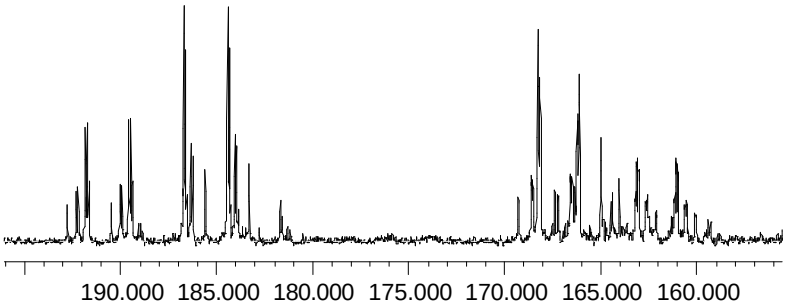
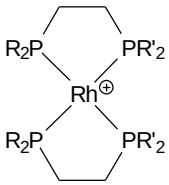
*Figure 3. Rh complex of phosphine **2**?*



A few trial simulations show that the spectrum can be explained by an AA'BB'X system (with X = Rh), and accurate coupling constants can be obtained by iteration (see Figure 4). Attempts to reproduce the spectrum using A_2B_2X or AA'BB'XX' systems were unsuccessful. This, in combination with the numerical values of the coupling constants, shows that the product is a *cis* bis(diphosphine) complex ***2a***.



2a

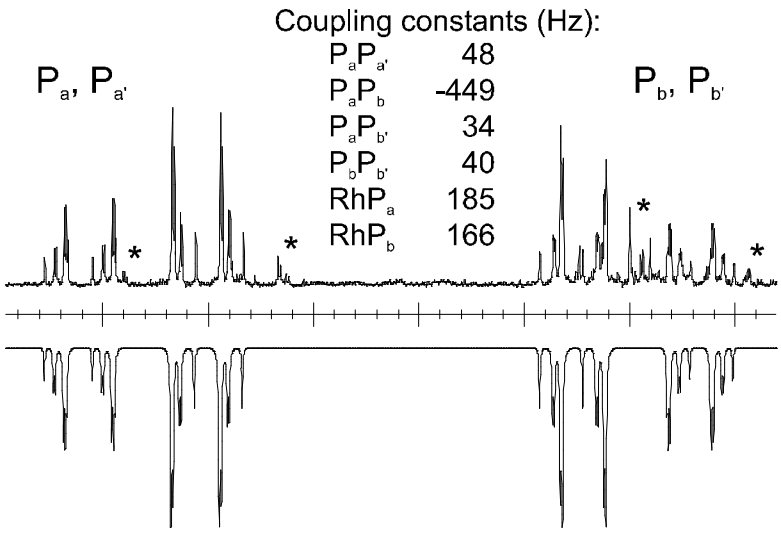


*Figure 4. Observed and simulated spectrum of complex **2a**, and parameters used in the simulation.*

Example 4. Dynamic behaviour of 1,6;8,13-*anti*-bis(methano)-[14]annulene.

Compound ***3*** has a temperature-dependent NMR spectrum (Figure 5).[1] It seems reasonable to explain this behavior by "freezing out" of the double-bond shift in ***3*** at low temperature. Is this explanation correct, and if so, can we extract the rates at different temperatures?

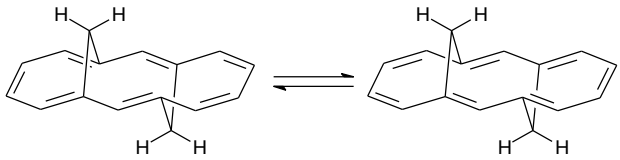


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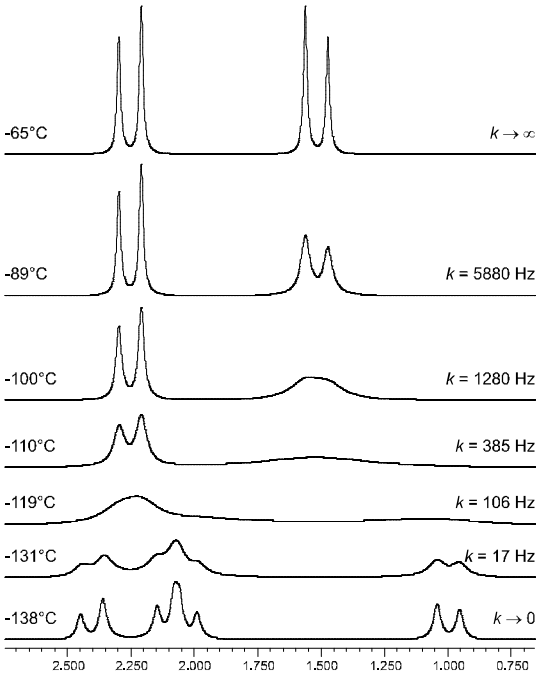
*Figure 5. Temperature-dependent spectrum of annulene **3**.*



Simulation can be used to predict the appearance of the spectrum at different exchange rates, given the parameters for the non-exchanging system. The results show that the proposed process is indeed consistent with the observed spectra. Fitting produces the rates at different temperatures, from which the activation parameters can be deduced using e.g. Arrhenius or Eyring plots.

These examples demonstrate the usefulness of simulation in the analysis of NMR spectra. Simulation is by no means necessary for every analysis. But if you are uncertain whether a spectrum you have measured may really correspond to a particular structure, simulation can be an easy way of obtaining confirmation.

1.2. Overview

The remainder of this manual provides some background on the simulation of NMR spectra. It is not a textbook on NMR; if you do not understand the principles of NMR, you should consult a textbook before trying to read further. However, most of the aspects of NMR spectroscopy that are relevant to simulation will be touched upon.

Chapter 2 discusses the "spin system", the basic unit that determines the type of NMR spectrum. Chapter 3 then describes how a spectrum can be calculated from this basic information. Chapter 4 touches briefly on the prediction of spectral parameters from molecular structures. Chapter 5 gives hints on how to simulate spectra of large molecules. Chapter 6 explains what happens when the system being studied is undergoing chemical reactions on the NMR time-scale. Chapters 7 and 8 discusses the two iterative methods for obtaining accurate parameters from experimental spectra, and chapter 9 describes the error analysis applicable to both.

Simulation is generally only useful when you already have an experimental spectrum. Nowadays, NMR data are always recorded as FID signals. This means that they have to be processed in some way to convert them to a spectrum meaningful to humans. At the very least, this requires a Fourier transformation; apodization, resolution enhancement and corrections for various filters may also be needed. Data processing is described briefly in Chapter 10. Finally, we have collected in Appendix A a number of frequently encountered second-order spectrum types that may help you in the interpretation of your own spectra.

2. The spin system

2.1. Introduction

The information that is needed for an NMR simulation consists of a qualitative part and a quantitative part. Together, they form the "spin system".

The qualitative part is the "composition" of the system: the number and types of NMR-active nuclei, and their symmetry relations. If the structure of the molecule being studied is known, this part can usually be written out easily. When the molecular structure is not known, classification of the system is more difficult. In simple cases, the type of spin system can be recognized directly from the NMR spectrum (e.g., the distinctive pattern of an ethyl group, or the typical 6-line pattern of the X-part of an AA'X system). But most types of spin systems have too many independent parameters to have a distinctive, easily recognizable pattern. If you want to simulate a complicated spectrum of a completely unknown compound, you will often have to go through some trial and error as far as the type of spin system is concerned.

The quantitative part is the set of shifts and coupling constants (and possibly other relevant parameters like exchange rates). "Guessing" accurate values for shifts and coupling constants is not easy (see also chapter 4). But once you are close enough too see correspondences between calculated and experimental spectra, further optimization can usually be done by the computer.

It is important to note here that the appearance of the spectrum depends only on the spectral parameters (shifts and couplings), not directly on the structure. If two completely different chemical structures would accidentally give rise to the same set of spectral parameters, they would also produce the same NMR spectrum.

2.2. Magnetic equivalence

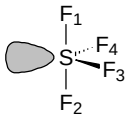
The concepts of magnetic and chemical equivalence are very important in NMR. Therefore, we will start with a formal definition of magnetic equivalence, and then use a few examples to illustrate the concept.

A group of two or more nuclei N_1-N_n are called magnetically equivalent if and only if:

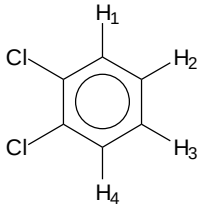
? All of the nuclei have the same chemical shift.

? For every individual nucleus M not belonging to the set N_1-N_n, the coupling constants J_{N1M}..J_{NnM} are equal. However, different couplings within the set are allowed, e.g. J_{N1N2} ? J_{N1N3}.

In principle, such a situation could occur by chance, but the term magnetic equivalence is usually reserved for those cases where there is a symmetry reason for the above conditions to hold. Let us consider two examples: sulfur tetrafluoride and *o*-dichlorobenzene.



SF_4 has a trigonal-bipyramidal structure, with one equatorial position occupied by a lone-pair orbital. As a consequence, it has two types of fluorine atoms: apical (1 and 2) and equatorial (3 and 4). The two apical fluorines have the same chemical shift ($?_1$? $?_2$), as do the equatorial ones ($?_3$? $?_4$), but $?_1$ will be different from $?_3$. Also by symmetry, all coupling constants between an apical and an equatorial fluorine are identical. Therefore, there are two groups of magnetically equivalent nuclei: the group of apical fluorines and the group of equatorial fluorines. This spin system is called an A_2B_2-system. Generally, a group of magnetically equivalent nuclei in a spin system (e.g. the group of two apical fluorines) is denoted by a capital letter (A) and a subscript (2) indicating the size of the group.[2]



o-Dichlorobenzene (ODCB) also has two groups of nuclei with identical chemical shifts: two *ortho* to a chlorine (1 and 4) and two *para* to a chlorine (2 and 3). However, nucleus 1 cannot be magnetically equivalent with 4, since J_{12} (an *ortho*-coupling) differs from J_{24} (a *meta*-coupling). It is not relevant here that J_{12} ? J_{34} and J_{13} ? J_{24}: as long as there is a single nucleus i for which J_{1i} ? J_{4i}, nuclei 1 and 4 cannot be magnetically equivalent. They are, however, called "chemically equivalent", as explained below. The ODCB-type spin system is usually called an AA'BB' or $[AB]_2$ system. Inequivalent nuclei that are related by a symmetry operation are usually indicated by a notation using primes, e.g. AA' for hydrogens 1 and 4. Note that the overall molecular symmetry of SF_4 and ODCB is the same (C_{2v}), so overall symmetry is not enough to determine magnetic equivalence.

> We will not discuss symmetry notations in detail here; for an excellent discussion, see Reference 3. C_{2v} indicates the presence of two mirror planes and a twofold axis, C_s means just a single mirror plane, and C_1 means no symmetry at all.

Magnetic equivalence is important because it allows considerable simplification in the calculation of NMR spectra. One of the reasons for this is a theorem which states that for any group of magnetically equivalent nuclei in a system, couplings within the group do not affect the spectrum and can be ignored. This means less typing for you, since you do not have to enter them. It can also be a disadvantage, since these constants cannot be determined from the experimental spectrum unless you reduce the symmetry of the molecule (e.g., by isotopic substitution). For example, the SF_4 spectrum is completely determined by two shifts ($?_1$ and $?_3$) and one coupling constant (J_{13}); J_{12} and J_{34} do not affect the spectrum and cannot be determined. In contrast, there are six relevant parameters in the ODCB system ($?_1$, $?_2$, J_{12}, J_{13}, J_{14} and J_{23}), and they can all be determined from the observed spectrum. The greater complexity of the AA'BB'-system is clearly illustrated in Figure 6.

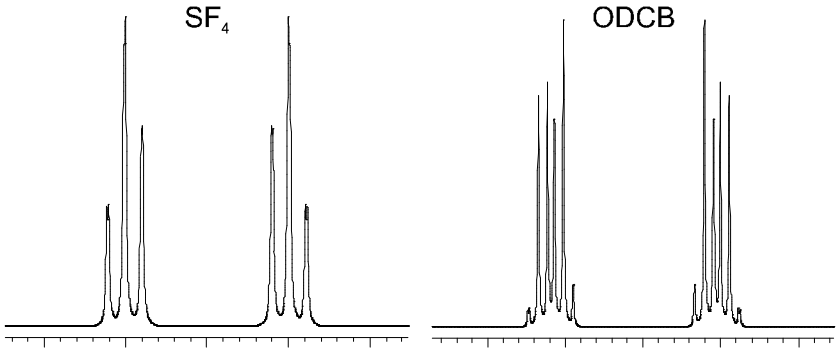


Figure 6. Spectra of SF_4 (left) and o-dichlorobenzene (right).

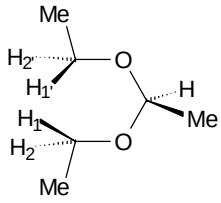
2.3. Chemical equivalence

Two or more nuclei are called "chemically equivalent" when they have the same chemical shift for reasons of symmetry. The values of coupling constants are not relevant to this definition, but the symmetry will in general imply some relationship between coupling constants involving chemically equivalent nuclei. Magnetic equivalence implies chemical equivalence, but not vice versa.

As an example, consider the four protons in the ODCB molecule discussed in the previous section. The molecule has C_{2v} symmetry, which causes H_1 and H_4 to have the same chemical shift (the same holds for H_2 and H_3). Thus, ODCB contains two groups of chemically, but not magnetically, equivalent protons. The molecular symmetry also implies that J_{13} ? J_{24} and J_{14} ? J_{23}.

The use of chemical equivalence (or symmetry in general) in NMR simulation can significantly reduce the computation involved. However, the full exploitation of symmetry is less trivial than that of magnetic equivalence, so not all simulation programs use full symmetry factorization.

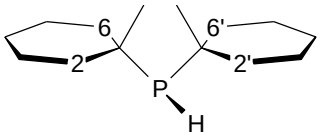
If nuclei are magnetically equivalent, they can be specified in groups, since they all have the same coupling constants to nuclei outside the group. Thus, you only have to specify a single entry for each magnetic-equivalence group instead of for each individual nucleus. Such a simplification is not possible for chemical equivalence, since different nuclei in a chemical-equivalence group may have different coupling constants to a single nucleus outside the group. Therefore, you will have to supply a separate entry for each nucleus in a chemical-equivalence group. You can, however, enforce symmetry by "linking" parameters (shifts, coupling constants) to ensure that, when you change one parameter, all symmetry-related parameters will also be changed.



It is not always trivial to decide whether two nuclei are chemically equivalent. Consider the methylene groups of acetaldehyde diethylacetal. This molecule has C_s symmetry, with a mirror plane bisecting the OCO angle. Reflection in this plane interchanges H_1 and $H_{1'}$, so these two hydrogens must be chemically equivalent. However, there is no symmetry operation that interconverts H_1 and H_2. These protons are diastereotopic. They not only have different chemical shifts, but will also differ in other chemical properties (for example, the rates of abstraction by a strong base will be different).

2.4. Temperature-dependent equivalence

The above discussion suggests that the classification of nuclei as chemically or magnetically equivalent is absolute, i.e. only dependent on the overall molecular structure. However, there are many examples of molecules which have a static low-temperature structure but acquire a higher effective symmetry at elevated temperature, usually through rapid inversion or rotation processes or chemical exchange (rate processes are discussed in more detail in chapter 6).



Consider a molecule of dicyclohexylphosphine. This has only C_s symmetry; the carbon atoms 2 and 6 of each cyclohexyl ring are diastereotopic (inequivalent), and the ^{13}C spectrum of a carefully purified sample at low temperature shows two distinct resonances for these two carbons. Addition of a trace of acid or raising the temperature results in rapid inversion at phosphorus via a protonation-deprotonation pathway. In the fast-exchange limit, the molecule has acquired effective C_{2v} symmetry; carbon atoms 2 and 6 have become equivalent, and only a single resonance is observed for these atoms.

A simpler example is the methyl group of an ethyl compound. In any static structure, it can have at most C_s symmetry, which would give rise to two separate resonances in the ratio 2:1. However, the barrier to methyl rotation is usually extremely low (<4 kcal/mol), so the rapid rotation occurring under most terrestrial conditions results in effective magnetic equivalence of the three methyl protons. Similarly, the three methyl groups of a *t*-butyl or trimethylsilyl group are usually equivalent.

2.5. Anisotropic spectra and full equivalence

So far, we have assumed that coupling constants are simply numbers. In fact, they are tensors and have an orientation-dependent term. In non-viscous solutions, however, the molecules tumble rapidly and have no preferred orientation, so we only see the average over all orientations (the "trace") of the coupling tensor, which is the number we call the (indirect or scalar) coupling constant J.

It is also possible to record NMR spectra of compounds dissolved in liquid crystals ("anisotropic media", hence the term "anisotropic spectra"). In such a medium, the molecules will not tumble completely randomly, but will have a preferred orientation with respect to the medium and to the external field. Because of this, the averaging of the coupling tensor is incomplete, and we also see a contribution of a second coupling, called the direct or dipolar coupling D. Dipolar couplings are usually much larger than indirect couplings. Because they provide information on the spatial positions of atoms, analysis of anisotropic spectra can yield direct structural information. This is a rather specialized topic: see Reference 4 for a more detailed discussion. To simulate anisotropic

spectra, you will have to supply direct (D) as well as indirect (J) coupling constants; if possible, you should extract the indirect couplings from isotropic spectra and fix them in anisotropic calculations.

In our discussion of magnetic equivalence earlier in this Chapter, we stated that couplings within a magnetic-equivalence group do not affect the spectrum. This is no longer true for anisotropic spectra. The indirect couplings J within the group are irrelevant, but the direct couplings D do contribute to the spectrum and must be included in the simulation. So, for anisotropic spectra the rules for equivalence are stricter:

? All of the N_1-N_n have the same chemical shift.

? For every individual nucleus M not belonging to the N_1-N_n, the coupling constants J_{N1M}..J_{NnM} and the D_{N1M}..D_{NnM} are equal.

? All D couplings within the group N_1-N_n are equal.

Groups of nuclei satisfying these criteria are called "fully equivalent". If you want to simulate anisotropic spectra, use the full-equivalence criterion to divide your spin system into equivalence groups. For example, the six protons of benzene are not fully equivalent, since D_{12} ? D_{13} ? D_{14}: you have to enter oriented benzene as a system of six separate (chemically equivalent) protons. However, ethane could be specified as two full-equivalence groups of three protons each. As an example, Figure 7 shows the simulated spectrum for benzene in an anisotropic medium, calculated with parameters given in Reference 4.

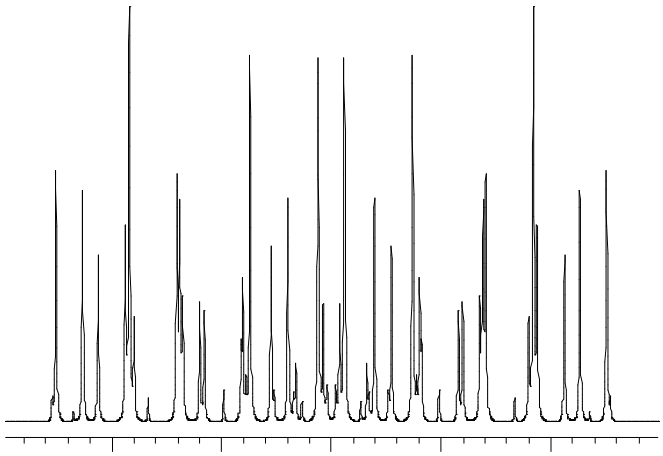


Figure 7. Anisotropic spectrum of benzene, obtained with J couplings of 8 / 2 / 0.5 Hz and D couplings of 333 / 64 / 42 Hz.

2.6. Shifts and coupling constants

The "chemical shift" ? of a nucleus is its resonance frequency relative to that of a particular reference compound. The shift is proportional to the external magnetic field, which is why shifts are usually expressed in ppm of the field: for different fields, they are constant when expressed in ppm, *not* when expressed in Hz. By convention, the sign of ? is chosen in such a way that higher ? values correspond to higher resonance frequencies. Also by convention, NMR spectra are written with ? values increasing from right to left.

> In principle, the chemical shift is a *tensor*, but in liquid NMR one usually just observes its trace, which is a *scalar* or number.

The magnitudes of chemical shifts are often discussed using a number of different terms, which correspond as follows:

low ? value	**high ? value**
low frequency	high frequency
high field	low field
high shielding	low shielding
shielded	deshielded
diamagnetic shift	paramagnetic shift

The "coupling constant" between two nuclei A and B is the energy difference between the situations where the two nuclei have parallel and antiparallel spins. More precisely, the energy contribution to the Hamiltonian is[5]

$$E_{AB} = h\, J_{AB}\, m_I(A)\, m_I(B)$$

From this equation, it is apparent that J > 0 implies the situation with parallel spins is higher in energy than the one with antiparallel spins. The energy difference is independent of the external field, so couplings are expressed in Hz. It is important to realize that (in contrast to e.g. infrared force constants) there is no general connection between coupling constants and bond strengths.

Shifts and couplings can usually be regarded as molecular properties. They are somewhat sensitive to temperature and solvent, but variations caused by the environment are usually small compared to the differences between different molecules. The most notable exceptions are observed for the chemical shifts of protons involved in hydrogen bridges.

Both chemical shifts and couplings can also usually be related to the direct environment (1-3 bonds) of the nucleus or pair of nuclei in question. In that sense, they are local probes of chemical structure. Particular orientations of bonds or ?-systems relative to a nucleus can cause longer-range effects on chemical shifts, and particular shapes of the bond path connecting two nuclei sometimes result in abnormally large long-range couplings. The prediction of NMR parameters from molecular structures is discussed briefly chapter 4.

2.7. The signs of coupling constants

NMR resonances are due to transitions between different spin states of nuclei. Coupling constants are a measure of the influence that the spin state of one nucleus has on the energy levels of another nucleus. A positive coupling constant implies that the nuclei prefer to have their spins antiparallel (?? or ??), and a negative coupling constant implies that they prefer to have their spins parallel (?? or ??).[5]

In general, it is difficult to determine the *absolute* sign of a coupling constant, but *relative* signs (i.e., relative to the signs of other coupling constants) can often be determined by several types of 1-D or 2-D experiments. It is possible to give rules for the signs of some types of coupling constants. For example, the geminal coupling of an aliphatic methylene group is usually negative; vicinal HCCH couplings are nearly always positive. For other types of couplings, however, the signs can vary from compound to compound.

If coupling constants can have either sign, the question arises whether these signs affect the appearance of the NMR spectrum. In general, spectra that are completely first-order are not affected by the signs of coupling constants. However, sign changes affect the peak labeling, which may be important in iteration. In spectra showing second-order effects, signs may be important. It is often true that there are groups of coupling constants which can change signs simultaneously without affecting the spectrum, whereas individual sign changes may produce a different spectrum. Before reporting the results of an iteration, it is important to check how many alternative sign combinations would also produce an acceptable (possibly identical) solution.

2.8. Isotopic substitution

Molecules of the same chemical composition but having a different isotopic composition are usually called isotopomers. The presence of different isotopes of a single element can give rise to a number of interesting effects in NMR spectroscopy.

To a very crude first approximation, the presence of an isotope does not disturb the shifts and coupling constants of the other nuclei in the molecule.

> This is really a rather crude approximation. Especially for nearest neighbors, the effect is often significant. Typical one-bond *isotope shifts* ? ? are -0.5 ppm in ^{13}C for CH? CD and -0.03 ppm in ^{31}P for P^{12}C? P^{13}C.

Also, the chemical shift of the isotope (expressed in ppm) will be approximately the same as that of the original nucleus in the original molecule, and coupling constants J_{XY} of any nucleus X to the isotope Y are related to the original coupling constants J_{XZ} via J_{XY}/J_{XZ} ? $?_Y/?_Z$. These relationships between isotopomers are not exact, because the presence of an isotope changes the vibrational levels of a molecule and the populations of different conformers.

Obviously, substitution of a single isotopic nucleus for one member of a magnetic-equivalence group destroys the equivalence. Couplings to the isotope can now be observed, and the above relationship can be used to estimate the coupling constants within the original group of equivalent nuclei. For example, substitution of one proton of a methyl group by deuterium allows observation of $^2J_{HD}$ and therefore estimation of $^2J_{HH}$ of the original methyl group as $^2J_{HH}$? 6.5?$^2J_{HD}$.

The presence of an isotope can also destroy the symmetry of a molecule in a more subtle way. For example, ethylene has four equivalent ^{1}H atoms, and the ^{1}H NMR spectrum shows just a singlet: no H-H coupling constants can be extracted. However, the presence of a single ^{13}C atom in this molecule lowers the symmetry and produces an AA'BB'X-type spectrum, from which all H-H and C-H coupling constants can be determined.

Symmetry reduction is particularly important in natural-abundance ^{13}C spectroscopy, when one usually looks at molecules having a single ^{13}C atom. Even if the original (all-^{12}C) molecule is symmetrical, many of its ^{13}C-isotopomers will not be symmetrical because the ^{13}C atom does not lie on all symmetry elements. This has noticeable consequences, particularly if there are other NMR-active nuclei in the molecule. For example, consider the diphosphine 1,3-bis(diphenylphosphino)propane and its 1-^{13}C and 2-^{13}C isotopomers. In the all-^{12}C species, the phosphorus atoms are equivalent. They are also equivalent in the 2-^{13}C isotopomer, and the ^{13}C resonance of C_2 will be a nice triplet. In the 1-^{13}C isotopomer, however, the phosphorus atoms are inequivalent, since the ^{13}C atom destroys the symmetry. The $^1J_{PC}$ coupling constant will be different from $^3J_{PC}$, and there will also be a small shift difference between the two phosphorus atoms. Therefore, the ^{13}C peak for C_1 will have a more complex splitting pattern. Very complex patterns can also be observed in ^{1}H-coupled ^{13}C spectra of symmetrical molecules.

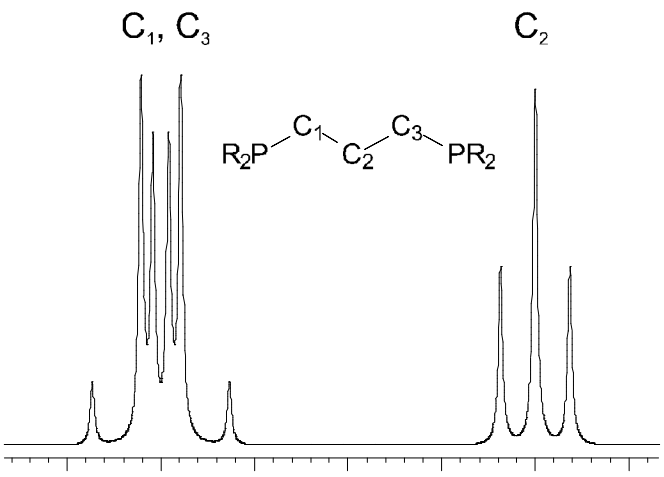


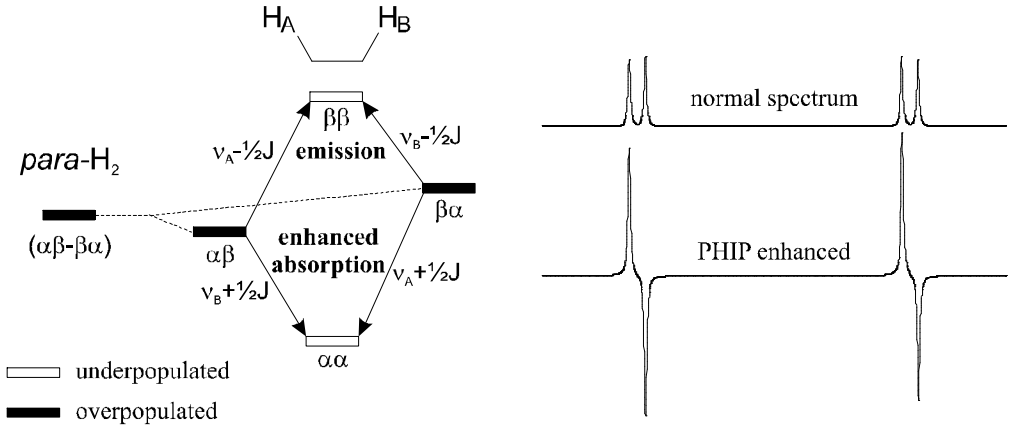
Figure 8. ^{13}C spectrum of a diphosphine.

2.9. Para-hydrogen induced polarization

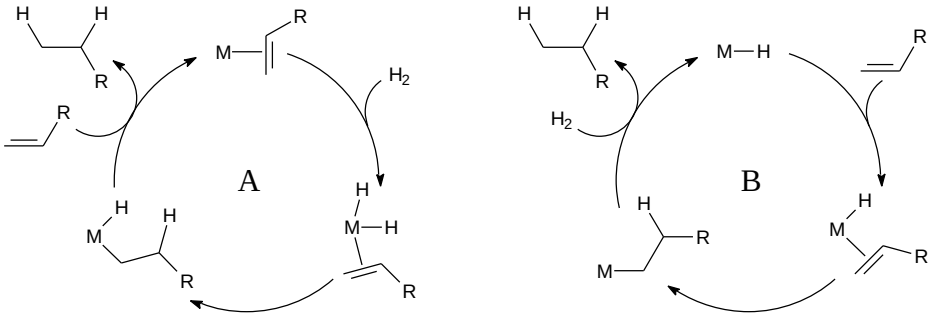
Over the last 15 years, para-hydrogen-induced polarization has become a very useful tool in the study of reactions involving molecular hydrogen (H_2).

H_2 always occurs as a mixture of *ortho* hydrogen (triplet: nuclear spins parallel) and *para* hydrogen (singlet: nuclear spins antiparallel). At room remperature, these species occur in a near-statistical (3:1) ratio. However, the energy difference between them is large enough that at low temperature the *para* state can become strongly dominant (e.g. 99.82% at 20K). Interconversion is slow in the absence of a catalyst. If a reaction is carried out with *para*-enriched hydrogen, and the two hydrogen atoms from a single hydrogen molecule end up coupled to each other in the same product molecule, spin states arising from them will have a non-Bolzmann distribution. This leads to large absorption and emission effects within multiplets (illustrated in Figure 9). The effect is called para-hydrogen-induced polarization (PHIP).[6,7] The spin states of the individual hydrogen atoms have a normal distribution (it is only their correlation that is non-Bolzmann), so that if the hydrogen atoms end up in different molecules, the effect is not observed.

Figure 9. Para-hydrogen-enhanced polarization.



PHIP can for example be used to differentiate between olefin hydrogenation mechanisms: hydrogen mechanism **A** will show PHIP, whereas hydride mechanism **B** will not.



The intensity enhancements caused by PHIP can be quite large, up to a factor of 10^3-10^4. This leads to a second application: detection of low-concentration intermediates in reactions of organometallic complexes with hydrogen.

The above explanation is not complete, and does not cover more subtle aspects of PHIP like net polarization effects and polarization transfer to other nuclei. For more complete descriptions and applications, see refs 8, 9, 10.

3. Simple simulation

3.1. Linewidths and lineshapes

So far, we have been discussing NMR spectra as if they were "stick" spectra, that could be fully characterized by a set of peak positions and intensities. Actually, peaks also have a particular *lineshape*.

In the case of a single nucleus resonating at a frequency f_0 with a relaxation behavior characterized by a single transverse relaxation time T_2, in the absence of saturation, the absorption lineshape is a pure Lorentzian with a width at half-height of $W_{½} = (?T_2)^{-1}$:

$$S(f) ? \frac{W}{?\frac{W}{2}?^2 ? (f ? f_0)^2}$$

In practice, however, ideal relaxation behavior is seldom observed. The actual linewidth is often dominated by field inhomogeneities, in which case the lineshape tends to resemble a Gaussian:

$$S(f)? \frac{1}{W} e^{?\ln 2 ? 2 \frac{f ? f_0}{W} ?^2}$$

Even under idealized conditions, both lineshape functions are strictly applicable only to either CW scans or to FT spectra *without* weighting. In practice, cleverly chosen weighting schemes are widely used to improve the appearance of NMR spectra, and such weighting may occasionally produce bizarre results, including lines complete with fake wiggles! Imperfect phasing may result in mix-in of dispersion components of the lineshape functions. Typical absorption and dispersion lineshapes (Lorentzian, Gaussian and triangular) are illustrated in Figure 10. In particular, note the extremely slow fall-off of the dispersion component of a Lorentzian away from its centre.

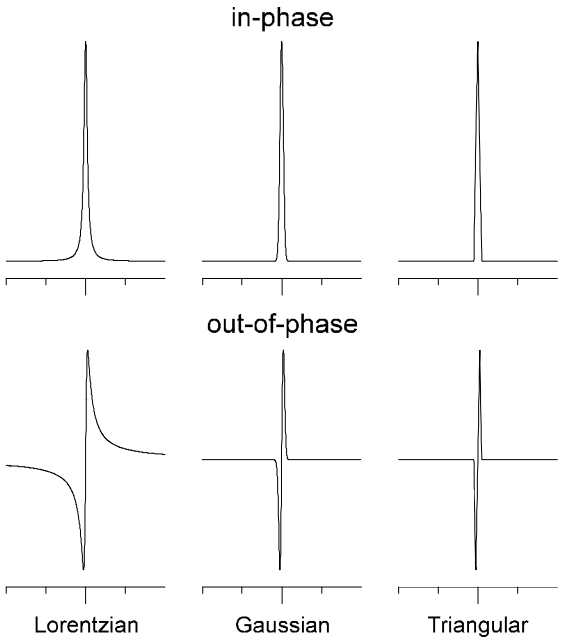


Figure 10. Examples of Lorentzian, Gaussian and Triangular lineshapes.

For systems consisting of many nuclei, most NMR simulation programs use just a single linewidth for the whole spectrum, which is often unsatisfactory. In practice, different nuclei can have very different relaxation times. Strictly speaking, it is not correct to assign a single relaxation time to each nucleus: relaxation processes of nuclei are often connected, and a "relaxation matrix" treatment is needed for an accurate description. In practice, however, having a single relaxation time per nucleus is usually satisfactory; exceptions occur in cases with

chemical exchange (see chapter 6) or with quadrupolar relaxation. There is no "clean" way of assigning a different relaxation time to each nucleus, short of the relaxation matrix treatment, which we want to avoid because it is too computationally expensive. Therefore, gNMR uses a more pragmatic solution and assigns to each peak a linewidth based on the "composition" of the corresponding transition, using a kind of population analysis. This appears to give satisfactory results even for strongly coupled nuclei with very different natural linewidths.

3.2. First-order spectra

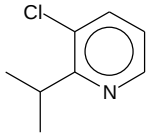
In simple cases, the appearance of an NMR spectrum can be predicted easily using the following rules:

? Every nucleus has a peak at its "resonance frequency", given by the chemical shift ?. The area of the peak is proportional to the number of nuclei.

? For every pair of spin-½ nuclei between which a coupling exists, both peaks are split into two components, with the same splitting J.

> If one of the nuclei has a spin ***I*** different from ½, it splits up the *other* peak into 2***I***+1 components.

Repeated application of these rules produces the familiar doublets, triplets, quartets etc. of high-resolution liquid NMR spectroscopy. If the nuclei are all of different types (e.g., ^{1}H and ^{31}P) these rules are virtually exact. For molecules containing several nuclei of the same type, small deviations are usually observed (mostly intensity changes).



Spectra that are (nearly) first-order are best interpreted "by hand". Chemical shifts are assigned from the centers of multiplets, and J couplings from the splittings. Comparison of splittings in different multiplets can be used to assign couplings to a specific pair of nuclei; small "thatch" effects may also be helpful here. As an example, Figure 11 shows the first-order analysis of the ^{1}H spectrum of 2-*iso*-propyl-3-chloro-pyridine.

In principle, this process could be automated. However, analysis programs get confused easily by partially overlapping lines in multiplets, and they also have a tendency to miss the weak outer lines of e.g. septets, which makes such automatic analysis unreliable. Simulation is generally not needed to analyze simple first-order spectra. In fact, the time required to set up the simulation may well exceed that needed to interpret the spectrum by hand.

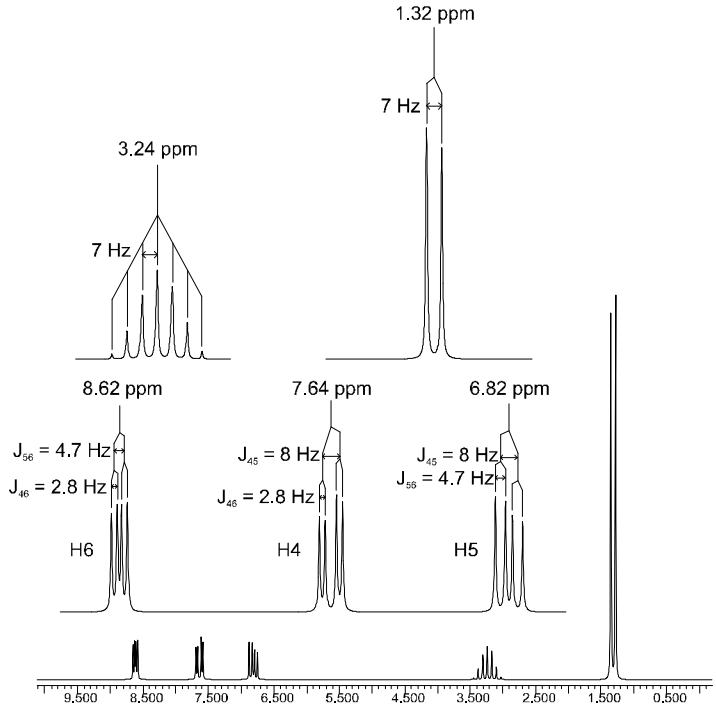


Figure 11. First-order analysis of ^1H NMR spectrum of 2-iso-propyl-3-chloro-pyridine.

3.3. Second-order effects

Second-order effects are all deviations from the simple rules for spectrum appearance mentioned above. The use of higher field strengths is often cited as the remedy for all second-order effects in NMR. Chemical-shift differences become large compared to coupling constants, so second-order effects will surely disappear. While this is an attractive argument for buying higher-frequency spectrometers, and for avoiding delving into NMR simulation, it is incorrect.

As a general rule, you will see second-order effects when the chemical-shift difference between two nuclei is of the same order of magnitude as the coupling constant between them (say, to within a factor of 10 either way). If the coupling constant is very small, the nuclei are "weakly coupled" and will give rise to a simple first-order spectrum. If the coupling constant is very large, the nuclei become effectively equivalent, again giving rise to a first-order spectrum. Second-order effects are expected in the intermediate range of "strong coupling". The first signs of second-order effects are usually small intensity distortions: inner lines become more intense at the expense of outer lines. If the coupling becomes stronger, the distortions become larger and extra splittings may appear. Also, second-order effects may appear on the multiplets of other nuclei in the molecule, even though these are not strongly coupled to any spin in the molecule.

Figure 12 illustrates what happens to an ABM system when the A and B nuclei go from a weakly coupled to a strongly coupled situation. In this series of spectra, the J_{AM} and J_{BM} couplings remain constant; only J_{AB} and ? ?$_{AB}$ change. Neverthless, the pattern observed for the M nucleus also changes.

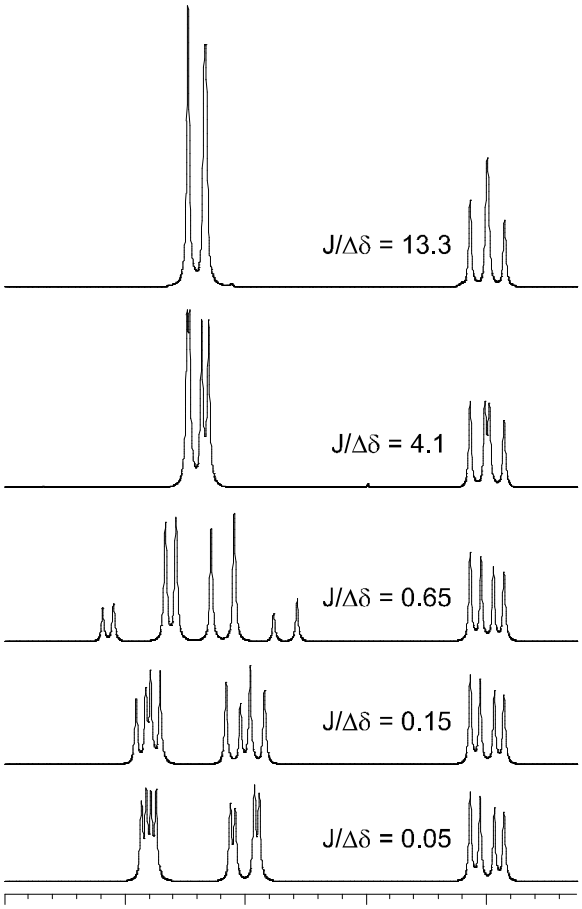


Figure 12. ABM system with constant J_{AM} and J_{BM} values, drawn for various values of $J_{AB}/?\,?_{AB}$.

If two nuclei are *magnetically* equivalent, you can treat them as a group: second-order effects will appear when coupling constants to nuclei outside the group become comparable to chemical-shift differences between these nuclei. Thus, the second-order effects in an A_2B_3 ethyl group depend on the ratio $J_{AB}/?\,?_{AB}$; both J_{AA} and J_{BB} are irrelevant.

If there are groups of *chemically* equivalent nuclei in the molecule, you can expect problems. The shift difference between the nuclei in the group is zero by symmetry, so there is no J/? ? rule to use. Instead, you can expect second-order effects when, for any nucleus X outside the group and two nuclei Y and Z inside the group, the ratio $r_X = J_{YZ}/?\,J_{XY}\text{-}J_{XZ}?$ is in the order of 1. If r_X is very small, you will see separate XY and XZ coupling constants; if r_X is very large, you will only see an average "virtual" coupling, and if r_X ? 1 you will see second-order complications. You can also expect second-order effects if r_X is very small for some X and very large for others, even if there is no X for which r_X ? 1.

To illustrate this, Figure 13 shows the ^{1}H spectrum of ODCB at different magnetic-field strengths. At low field, the inner lines are much more intense than the outer lines: this second-order effect is caused by the small chemical-shift difference between the two types of protons. For fields higher than *ca* 300 MHz, this effect has largely disappeared: the two multiplets are each approximately symmetrical. However, they are not simple doublets of doublets of doublets, and will not become so at any field: the small outer lines of each multiplet really belong to the spectrum and will not disappear. The criterion for second-order effects here, $r_1 = J_{23}/?\,J_{12}\text{-}J_{13}?\,? = 7.47/(8.14\text{-}1.49)$? 1, is fulfilled regardless of the external field. Therefore, interpretation of the splittings as coupling constants is not allowed, and will in fact produce completely incorrect values.

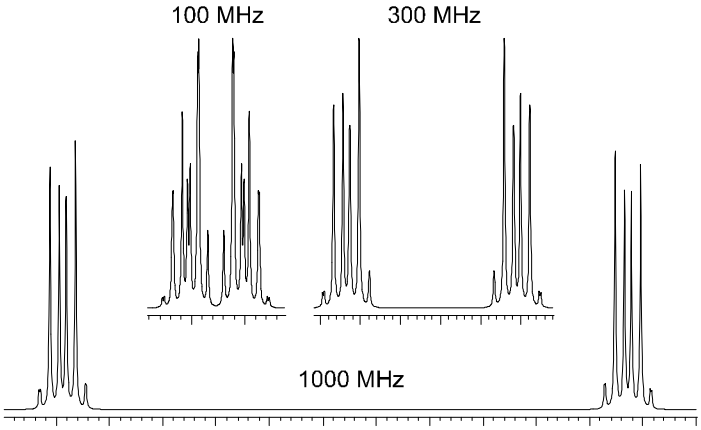


Figure 13. Calculated spectra of ODCB at different field strengths.

There is nothing mysterious about second-order effects. Their origin is completely understood, and any decent simulation program will produce the correct spectrum given the right parameters. However, interpretation of second-order spectra without a simulation program is difficult, since the human mind and eye are simply not well suited to the recognition of patterns of matrix eigenvalues. Therefore, simulation is an indispensable tool for the interpretation of second-order spectra.

4. Prediction of parameters from molecular structure

It would be nice if it were possible to predict chemical shifts and coupling constants from a given molecular structure. Unfortunately, this is not generally possible at present, although some significant advances have been made in recent years. There are two different ways to approach the problem: empirical methods (based on measured data) and theoretical methods (based on quantum-chemical calculations).

? **Empirical methods**
Using a database containing many known compounds with their NMR data, it is possible to estimate data for related but unknown compounds using various statistical methods and structure-property relationships. The accuracy of this method depends strongly on the quality and size of the set of reference data.
Clearly, it is impossible to predict data for compounds with very abnormal structures or interactions in this way. Accurate prediction is now possible for ^{1}H and ^{13}C shifts and couplings of "normal" organic compounds, and database-based prediction programs for ^{19}F and ^{31}P have recently started to appear. Predictions of metal NMR shifts is not yet available, partly because of the lack of sufficient reference data and partly because there is not enough (commercial) interest.

? **Theoretical methods**
Ab initio calculation of coupling constants is possible but requires large basis sets and advanced electron correlation treatments. Chemical shifts can be calculated with reasonable accuracy (a few ppm for heavy atoms, or ?0.5 ppm for hydrogen), but this requires the use of optimized structures and polarized basis sets. Due to increases in computer power and sophistication of algorithms over recent years, ^{13}C, ^{19}F and ^{31}P shift calculations for organic molecules have now become more or less routine.
At least as important as the computational problems of the theoretical approach are the chemical ones. NMR parameters are the time-averaged values over all accessible conformations of a molecule, and often also include significant contributions due to interaction with the solvent. Therefore, accurate prediction from theory alone is at least an order of magnitude more complicated than just a single IGLO or GIAO calculation. The main advantage of the theoretical method is that it allows predictions for exotic structures as well as for "normal" organic molecules.
As an alternative to the rather expensive *ab-initio* method, prediction using semi-empirical methods has also been attempted. Extensive parametrization is required to make this work, including classification of "atom types". Therefore, this method, is again unsuitable for unusual bonding situations or non-standard nuclei. However, it may be a useful addition to the database approach mentioned above.

If one doesn't set the sights too high, simple additivity rules for chemical shifts can produce quite reasonable results. We have found the rules given by Pretsch[11] quite useful, but other good collections exist. Coupling constants are strongly conformation dependent, but for most common cases this dependence is well documented (if not completely understood), so if the 3D structure of a molecule is known (short-range) couplings can be estimated with reasonable accuracy. Abnormally large long-range couplings are nearly always associated with particular geometries of the bond path ("zigzag" or W paths), or with very short through-space contacts; prediction of the magnitude of such couplings is difficult.

5. Simulating large systems

5.1. On the scaling of NMR calculations

In principle NMR simulation is simple. Set up the Hamiltonian, diagonalize to get the energy levels, multiply eigenvectors with transition moments to get intensities, evaluate a Lorentzian for every calculated peak...

Unfortunately, the scaling of the calculation is rather unpleasant. The size of the calculation (dimension of the Hamiltonian) scales as $\binom{n}{n/2} \approx 2^{n-2}$, the storage requirements as the square of this, and the computing time as its cube. For every nucleus added to the system, the time required increases with a *factor* of 8! This makes calculations for large molecules (> 12-15 atoms) rather difficult. For example, on a 100 MHz Pentium a particular 6-spin problem took 0.1 seconds to simulate, an analogous 8-spin problem 0.73 seconds, the 10-spin problem 22 seconds, and the 12-spin problem 27 *minutes*. With the current rates of increase of CPU speed (a factor of 2 every 1-2 years), it will be several decades before we can do 25-spin systems! This is the reason many NMR simulation programs won't let you simulate systems larger than 8-10 spins. Or if they do, the spectrum is often evaluated by first-order methods, which are rarely good enough.

There are several methods for reducing the computation requirements of a simulation. Some of these can be carried out automatically by the simulation program, and some can be done by the user, as detailed in the next two sections. But none of these will help with the simulation of really large systems (say, larger than 15 nuclei). To handle such systems, one must resort to approximate calculations, and that is the topic of the final section of this chapter.

5.2. Simplification by the simulation program

The following techniques can be applied automatically to reduce the size of an NMR simulation without any loss of accuracy:

- Splitting of the system into uncoupled fragments if possible.
- Detection of magnetic equivalence, and treating of groups of magnetically equivalent nuclei as composite particles.
- Detection and use of full molecular symmetry (chemical equivalence).
- Division of the system into "X-groups" for nuclei of different types.

Splitting a system can result in huge savings of computation time. The other techniques will only result in a modest reduction of the size of the calculation. Nevertheless, it is worthwhile to exploit them whenever possible.

If the result need not be exact (but still rather good), it is possible to use the technique of "X-group" division between nuclei of the same type. This will introduce errors, but as long as the groups are only weakly coupled most errors can be eliminated by the use of perturbation theory to handle the interaction between these groups. Perturbation theory does not result in large savings, but - like the other techniques mentioned above - it can make the difference between a feasible simulation and an impossible one.

5.3. Simplification by the user

Unlike a simulation program, you as user know what is really interesting about a particular spectrum. Therefore, you can take more drastic measures to reduce the size of a simulation:

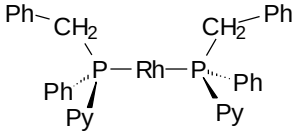
? Delete parts of the molecule remote to the fragment of interest.

? If you are interested in a molecule having several equivalent fragments, use only one such fragment and if necessary "terminate" it with an innocent end-group.

? Set very small couplings between nuclei in different fragments to zero, so that the simulation program can divide the molecule into uncoupled fragments.

These measures will all change the simulated spectrum, unlike the ones mentioned in the previous section. Therefore, it would be unwise to let the program apply them automatically. And if you apply them yourself, you should always try to check whether the simplifications were justified. For the correct simulation of second-order systems, you often need to include more than just the nuclei that couple directly to the fragment of interest.

As an example, let us try to reproduce the methylene group signals of bis(benzylphosphine)rhodium complex ***4*** (experimental spectrum shown in Figure 14A). The two protons of each methylene group are diastereotopic, so we will need at least these two protons, a phosphorus atom, and the rhodium atom (the Rh-H couplings are not zero). This gives a 4-spin H_2PRh system. However, even the best simulation (Figure 14B) comes nowhere near the experimental result.



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The $^2J_{PP}$ coupling is fairly large (43 Hz), so we may have to include the second phosphorus atom. In that case, we will also have to include the second CH_2 group. If we did not do so, the phosphorus atoms would become very different, and the results might not be meaningful. The system is now a 7-spin H_4P_2Rh system, already rather large, but the simulation (Figure 14C) is still unable to reproduce the curious pattern of the experimental spectrum, although it starts to look reasonable. What can be missing here?

There are no significant couplings from the methylene group to the benzylic phenyl group, so the problem must be somewhere else. It turns out that extra couplings to the phosphorus atoms are needed to get the pattern of Figure 14A. These couplings are really there: the phenyl and pyridyl protons all have significant phosphorus couplings. What is surprising is that you would need them to reproduce the benzylic methylene signal. Luckily, you do not need *all* the phenyl and pyridyl protons in the simulation. Figure 14D shows the simulation of Figure 14C with just one hydrogen atom added per phosphorus atom (J_{PH} = 20 Hz). This is a 9-spin H_6P_2Rh system, fairly large indeed, but the pattern finally looks correct. Of course, the addition of a single P-H coupling to represent the effect of one phenyl and one pyridyl ring looks a bit like fudging. Clearly, any coupling constant fitted for it will be meaningless, and some other parameters may not be very significant either. However, the exercise illustrates that you really can get the curious resonance shape of Figure 14A from the structure shown above.

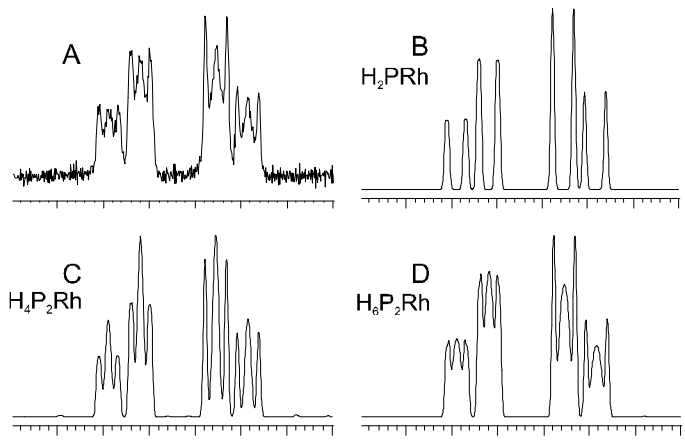


*Figure 14. Methylene resonance of **4** (A), simulated with increasingly complicated spin systems (B-D).*

5.4. Approximate calculations

As mentioned earlier, for really large molecules exact simulation is impossible, so one is forced to resort to some sort of approximate calculation. The most drastic approach is simple first-order calculation (see section 3.2), possibly with some cosmetic corrections to reproduce "thatch effects". This is certainly extremely fast, but is only good for near-first-order spectra, for which one usually doesn't need simulation anyway.

Here we propose an intermediate scheme based on a "divide-and-conquer". It has been implemented in gNMR and appears to work satisfactorily in most cases.

The design of the algorithm is based on the way one normally does the analysis of a spectrum. Whereas a simulation program calculates the whole spectrum at once, a chemist will look at each individual multiplet in turn. Direct couplings to the nucleus in question are considered first (the "first shell"). If there are other nuclei that don't couple directly with the target nucleus but do couple strongly to other nuclei in the "first shell", second-order effects will occur (e.g., "virtual triplets"), and these nuclei are also required to understand the spectrum (the "second shell"). One could go further, but in practice two "shells" are usually sufficient to explain the shape of a multiplet.

This suggests that the simulation should also calculate the multiplets one by one, using only as much of the environment as is needed to reproduce the patterns. The problem is that simulation of a part of a molecule will not only produce the target multiplet (which is presumably accurate), but also resonances due to the "shells", which are probably very inaccurate. The key point of the approximate approach is that the simulation is indeed done in chunks, but from each chunk spectrum everything is thrown away that is not due to its target nucleus; then the chunk spectra are added to give the final spectrum. The technical details can become a bit complex but are not important here.

The key advantage of this scheme is that it scales linearly in system size, which means that future increases in CPU speed will immediately result in the ability to simulate significantly larger systems. The minimum chunk size needed to obtain correct multiplet patterns is usually 8-9 nuclei, so the break-even point of this method appears to be in the range of 11-12 nuclei, i.e. close to the maximum that can be handled by "exact" simulation anyway. As an illustration, Figure 15 shows a fairly complex spectrum (14 spins) simulated exactly and with the "shell" method. For smaller systems, exact simulation is still the method of choice.

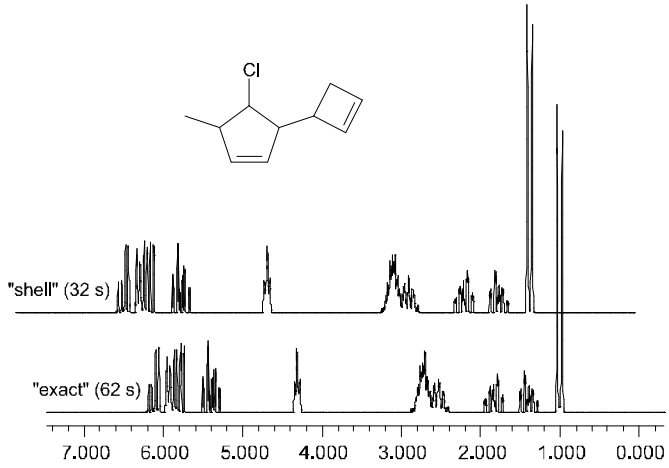


Figure 15. ^{1}H spectrum of a fairly large organic molecule, simulated using "exact" (top) and "shell" (bottom) methods.

6. Chemical exchange

6.1. The effects of chemical exchange

In contrast to many other spectroscopic methods, where kinetics can only be used to study irreversible reactions, NMR can also be used for kinetic studies of systems in equilibrium. This is because the NMR time-scale, of the order of milliseconds or microseconds, is conveniently close to our own time-scale. Reversible processes with activation energies of the order of 5-20 kcal/mol can be studied by "band-shape analysis", explained below.[12] For reactions with slightly higher barriers, techniques like polarization transfer may be more appropriate.

As an illustration of an exchange process, let us consider Me_2NPF_4, which has been studied by Whitesides[13] (we have modified a few parameters from the data given by Whitesides to make the example more illustrative). This has a trigonal-bipyramidal structure, with the amino group in the equatorial plane. There are two groups of magnetically equivalent fluorine atoms, as in the SF_4 example discussed earlier. Since the phosphorus atom is also magnetically active, we can characterize this molecule as an A_2B_2X system (ignoring the dimethylamino group). The low-temperature ^{31}P spectrum (a triplet of triplets, Figure 16A) can indeed be interpreted in this way. However, at higher temperatures the fluorine atoms start to exchange. In the high-temperature limiting spectrum (also called the "fast-exchange limit"), the spectrum shows just the quintet of an A_4X system (Figure 16D): the fluorine atoms have become equivalent "on the NMR time-scale". What happens is that the exchange is so much faster than the actual NMR experiment that we observe the time-averaged situation.

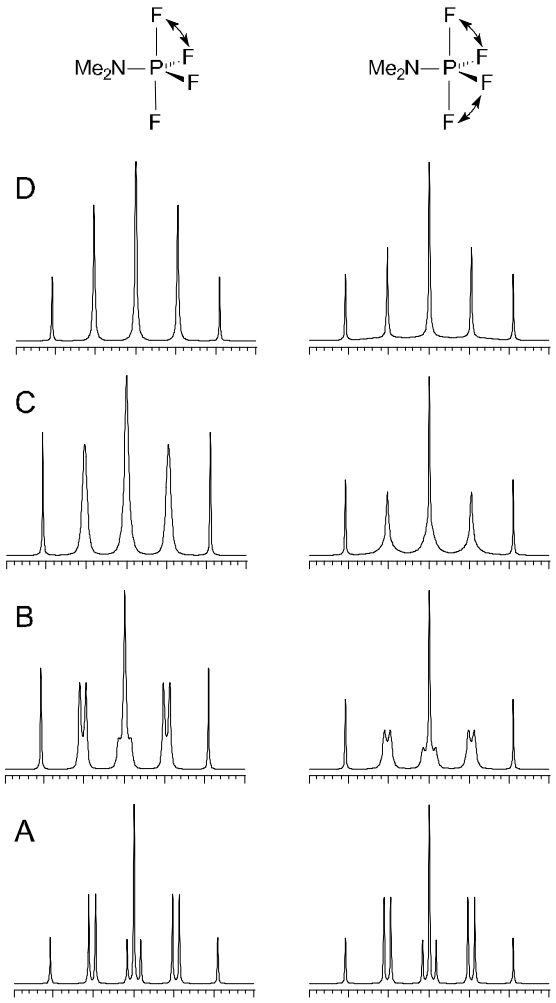
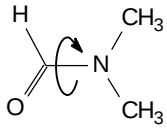


Figure 16. One-pair (left) and two-pair (right) exchange $^{31}P\{^1H\}$ spectra for Me_2NPF_4.

Neither the low-temperature (or "slow-exchange") limit nor the high-temperature limit is particularly interesting: the interesting things happen in between. As the temperature is raised, the initially sharp lines (Figure 16A) broaden and coalesce (Figure 16B, C) until, in the fast-exchange limit, a sharp spectrum is obtained again (Figure 16D). For the intermediate situations, it is possible to determine a rate constant from the line broadening by fitting. The temperature dependence of the rate constant can then be used to extract activation energies and entropies. Moreover, different exchange mechanisms may give rise to different line broadening patterns in intermediate situations, even though the fast-exchange limits are the same. If these differences are large enough (as they are in Figure 16), it will be possible to distinguish between such mechanisms; in the particular case discussed here, the reaction was clearly shown to follow a two-pair exchange pathway.

6.2. Intra- and inter-molecular exchange

Actually, the terms intra- and inter-molecular exchange are slightly misleading, because their normal chemical meaning is not entirely appropriate to NMR. The distinctions needed to understand dynamic behavior are more subtle. Four typical examples are illustrated below.



We will start with the simplest case, which is often called *intramolecular mutual exchange*, and will use dimethylformamide as an example. The dynamic behavior shown by this molecule (Figure 17A) is hindered rotation around the amide bond. At low temperature (bottom trace), you will see two different methyl resonances in the ^{1}H spectrum. On raising the temperature, they broaden and then coalesce to a single peak. In effect, all six protons of the methyl groups have become magnetically equivalent on the NMR time-scale. The position of the single peak corresponds (approximately) to the average of the chemical shifts of the individual methyl groups. If there had been any observable couplings from the methyl groups to other parts of the molecule, the high-temperature limit would also show averages of these coupling constants. The Me_2NPF_4 example discussed above also showed such an exchange in its ^{31}P spectrum.

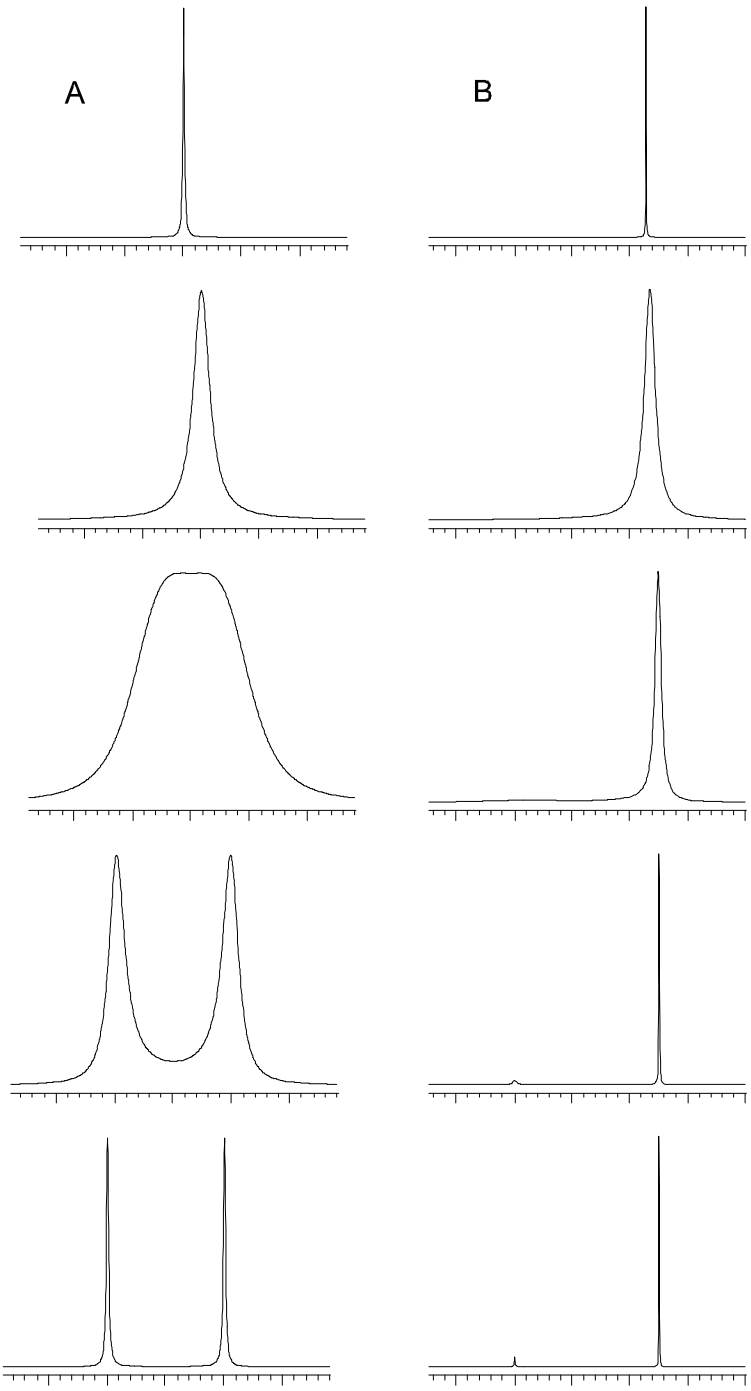
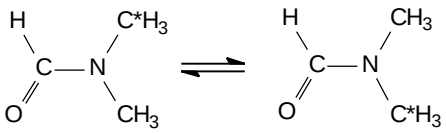
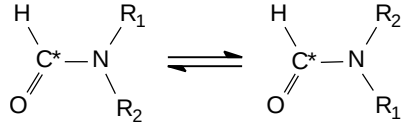


*Figure 17. Effect of hindered C-N rotation on (**A**) HCON(C**H**$_3$)$_2$ and (**B**) H**C**ON(R1)(R2).*

Now consider the ^{13}C spectrum of the same compound. At low temperature, we actually have two different "molecules": one with a ^{13}C atom *trans* to oxygen, and one with the ^{13}C atom *cis* to oxygen. (We are ignoring molecules containing two or more ^{13}C atoms because their abundance will be negligible). This type of exchange is called *intramolecular non-mutual exchange*. For this particular case, the resulting spectrum will still be rather similar to the ^{1}H example described above, but the distinction between mutual exchange (*within* a single species) and non-mutual exchange (exchange *of species*) is important.



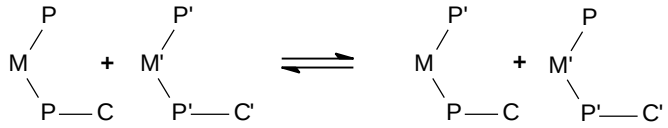
We can carry this point further by looking at the isomerization of an amide with different organic groups at the nitrogen. Let us consider only the ^{13}C resonance of the carbonyl carbon. Since the two organic groups in our hypothetical amide are different in size, there will be an



energy difference between the *cis*- and *trans*-isomers: the equilibrium will contain (say) 10% *cis* and 90% *trans*.

Figure 17B shows the (simulated) behavior. Note that, at equilibrium, the forward and backward reaction rates are equal. This implies that the rate constant of disappearance of the *cis* isomer, $\boldsymbol{k}_{cis?\ trans}$ = Rate/[*cis*], is much larger than the rate constant of disappearance of the *trans* isomer, $\boldsymbol{k}_{trans?\ cis}$ = Rate/[*trans*]. Therefore, line broadening for the *cis* isomer starts at a lower temperature than for the *trans* isomer: the process does not look very symmetric. The high-temperature effective chemical shift is an average (weighted by the concentrations) of the separate low-temperature chemical shifts; if there were any coupling constants, these would become weighted averages as well.

Finally, we will consider an example of what is commonly called *intermolecular exchange*, using a hypothetical metal-bis(phosphine) complex as an example.



This example, which shows a curious rate dependence of the NMR signal, was first described by Swift (Reference 14). Figure 18 shows the theoretical ^{13}C resonance of a carbon atom of the phosphine ligand as a function of the exchange rate of the phosphines.

At low exchange rates, the spectrum is a virtual triplet, because J_{PP} is large. At high exchange rates, the ^{13}C atom only "sees" the phosphorus atom in its own ligand molecule, so the spectrum is a nice doublet. At intermediate exchange rates, something curious happens: it looks as if there is only a (broad) singlet! Not all intermolecular exchange processes show such strange behavior, but it is important to remember that predicting the appearance of dynamic spectra can be difficult.

The loss of coupling constant information is often taken as proof of an intermolecular process. For example, if you observe the disappearance of the ^{183}W satellites on the ^{31}P signal of a tungsten-phosphine complex, you may well be looking at a phosphine exchange process. This is not an absolute proof, since intramolecular averaging of positive and negative coupling constants may also lead to near-zero values, but it is a reasonably strong indication.

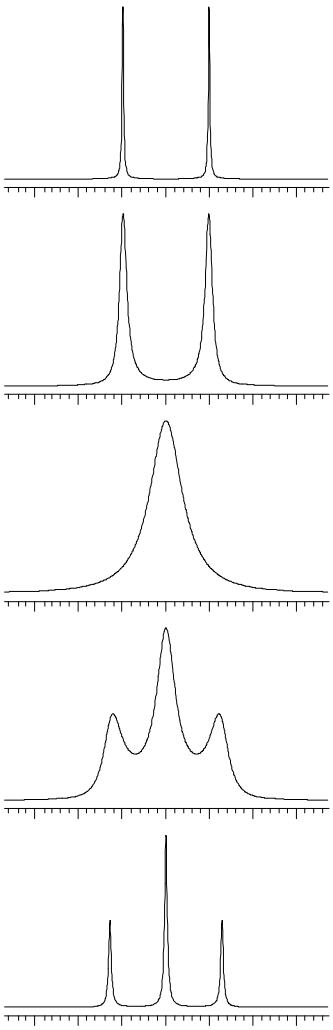


Figure 18. A-part of exchanging AXX'-system with J_{AX} = 10, $J_{AX'}$ = 3 and $J_{XX'}$ = 50 Hz.

As far as NMR is concerned, the meaning of "intermolecular" only relates to the collection of nuclei you are observing in a specific reaction. The reaction would be called *intra*molecular if this collection stayed together, regardless of whether the reaction is caused by *inter*molecular exchange involving other parts of the molecule. For example, the allylic bromine exchange shown below is intramolecular as far as NMR is concerned (since bromine is not NMR-active). However, the dependence of exchange rate on bromine concentration could reveal the bimolecular nature of the reaction. This once again illustrates that one should be very careful in discussing the nature of rate processes using NMR data.

6.3. Interpretation of exchange rates

It will be clear that band-shape analysis can be a powerful mechanistic probe. Qualitative information (distinction between mechanisms) can be obtained from inspection of fitted results. Quantitative data (activation parameters) can be determined from Arrhenius and/or Eyring plots using fitted rates. There are, however, a number of potential pitfalls:

? Small line broadenings, as observed near the slow- and fast-exchange limits, can be caused by a large number of factors, and exchange is only one of them. Therefore, rate constants determined near these limits are necessarily rather inaccurate.

? Chemical shifts often show a marked temperature-dependence. If the signals that are coalescing in the exchange process are close together to begin with, this may result in large errors in the fitted rate constants. In principle, it is possible to fit chemical shifts and rate constants simultaneously, but near coalescence there will always be a high correlation

between the two, which makes such an optimization risky. Coupling constants are much less temperature-dependent: they should be determined from the slow-exchange spectrum and fixed for subsequent fits.

? The predicted differences in coalescence behavior for different mechanisms are seldom as obvious as those illustrated above. One should not be overly optimistic in distinguishing between mechanisms.

? Small amounts of impurities may have a large effect on reaction rates. Also, impurities may cause new exchange mechanisms competing with the one you are trying to observe. This may lead to completely erroneous interpretations of the results. Occasionally, you may encounter dynamic behavior in a situation where an equilibrium strongly favors one side. You may never directly observe the minority species, because its concentration is too low at all temperatures, and still see some kind of coalescence behavior in the majority species. Such spectra can be very difficult to interpret correctly.

? Band-shape analysis produces "pseudo-first-order rate constants". How these actually relate to the "real" rate constants for the process you are interested in depends on the model you use for the reaction. The relation can already be nontrivial for *intra*-molecular mutual-exchange processes;[15] for *inter*-molecular processes it be even more complicated.

? There may be more than one dynamic process occurring in the system. It is often easy to distinguish between an *inter*- and an *intra*-molecular process, but if you suspect the occurrence of several intra-molecular processes, only the difference in computed rate constants may be able to prove your case. Since the errors in rate constants are always rather large (regardless of what an optimistic fit program may tell you), you should be very careful not to assume several processes where only one is really needed (Occam's razor). Note that a difference in coalescence temperatures does *not* imply a difference in rate constants.

7. Iteration with assignments

7.1. Description

Iterative optimization of shifts and coupling constants by computer was first implemented by Alexander[16] and Swalen and Reilly[17] using a scheme based on the determination of energy levels. Several modifications to the scheme were subsequently implemented, but the most important improvement was introduced by Bothner-By and Castellano[18] and Braillon:[19] they decided to use the observed frequencies as the basis for a least-squares optimization. Various refinements of the method have been described since, including the use of magnetic equivalence, molecular symmetry, and anisotropy, but the principle of the method has hardly changed. The user must start with an initial guess of shifts and coupling constants, calculate a spectrum, and then decide which lines in the calculated spectrum correspond to which lines in the experimental spectrum (this phase is called the "assignment" phase). After that, the computer performs least-squares minimization, and the user checks whether the results seem reasonable, either by comparing the calculated and experimental spectra, or by inspecting the list of calculated and observed frequencies.

7.2. Pros and cons of assignment iteration

The assignment iteration method has been in use for many years and is still useful, especially for small molecules. However, it has a number of disadvantages:

? It requires a good guess of starting values for the shifts and coupling constants. If the initial guess is not good enough, you will not be able to assign most peaks correctly, and the optimization will not produce useful results.

? For large systems, assigning peaks can become very tedious. For example, a 6-spin system without symmetry will have about 200 peaks (not counting the combination lines), and assigning even the majority of these will be rather awkward and time-consuming, however helpful the software tries to be in the process. Moreover, the chances are that many of these lines will partly overlap, so the assignment will not be very accurate. This introduces an arbitrariness in the results, and the final optimized parameters will contain systematic errors which are not reflected in an error analysis.

? You can iterate only on shifts and coupling constants, not on linewidths or rate constants. Thus, on completion of the iteration your result may not look as good as when you had carried out a full-lineshape analysis (next chapter), even though the agreement in peak positions is perfect.

? Intensity data are not used in the calculation. There are cases where peak positions alone do not determine all relevant parameters (the X-part of the simple AA'X-system is an example).

> The last objection is not insurmountable. Arata *et al* previously proposed including intensity data in the iteration scheme[20] although they did not actually implement such a scheme. gNMR is probably the first simulation program to incorporate this possibility.

More importantly, for some spectra there are several distinct, well-determined solutions giving exactly the same set of peak positions but with different distributions of intensities. Clearly, there is no way that iteration on peak positions is going to distinguish between such solutions.

The assignment iteration scheme also has some advantages:

? It is fast.

? It gives the user a fair degree of control over where the iteration is going.

? You do not have to import an experimental spectrum to start the analysis: a peak list is enough. For large systems, typing in a peak list may be tedious, but for small systems retyping a few numbers may be more efficient than transferring the whole spectrum. Also, the spectrum is sometimes not available in electronic form.

? You can iterate on very noisy spectra, or spectra showing impurities and baseline errors, where full-lineshape analysis would not work at all.

So, for small systems with not too many lines, assignment iteration can be the method of choice. For larger systems with many independent parameters, where a good initial guess is difficult to obtain anyway, full-lineshape analysis is recommended.

7.3. Why the computer cannot do the assignments

The assignment phase of assignment iteration seems rather trivial: you could just let the computer assign the peaks in order of their occurrence in the spectrum. So why doesn't this work, and why do you have to do the assigning?

> There are already some fairly sophisticated computer algorithms for automatic peak assignment.[23] However, they are far from foolproof, and doing it yourself is still the best way.

The first problem is that there is seldom a 1:1 correspondence between calculated and experimental peaks. A single observed peak may be due to a number of contributing elementary transitions. The simulation program yields them as distinct peaks, but there is no general way to tell from an experimental spectrum whether a peak is single or composite. Also, some peaks may have such a low intensity that you simply do not see them in the experimental spectrum.

The second problem is that, even if the computer recognizes the correct number of peaks in the experimental spectrum, assigning them in order may not be correct. Every peak in the spectrum consists of a well-defined transition (for example, ???? ???). The ordering of the peaks depends on the parameter values: the ???? ??? transition might be at higher field than ???? ??? for a certain J_{12} value, and at lower field for another value of this constant. There is no direct way to tell from the experimental spectrum which is which, but the iteration algorithm needs this information (compare this with the phase problem in X-ray crystallography). This is where human input is needed: by telling the program which experimental peak corresponds to a calculated peak, you assign a composition to the peak. With that information, the program can do the iteration.

Now it will also be clear why you need good starting values for assignment iteration: without a good start, you will not be able to recognize patterns and make the right assignments. The convergence of the iteration after assignments are done is much less of a problem.

If you change the signs of one or more coupling constants in the system, the overall spectrum often remains (nearly) the same, but the compositions of individual transitions change. Therefore, you will have to redo assignments after such a change if you want to try different sign combinations. Simply changing a sign and restarting the iteration usually doesn't produce a new solution but only restores the original sign.

8. Full-lineshape iteration

8.1. Description

An obvious alternative to the method of assignment iteration described above would be to do a direct least-squares iteration on the full experimental spectrum. However, unless you have an extremely good initial guess of parameters, a direct least-squares fit of an observed to a calculated NMR spectrum is unlikely to converge to the correct parameter values. The reason for this is that usually the $?^2$ error function has many local minima surrounding the global minimum, and the direct optimization is likely to get "trapped" in such a local minimum before it ever reaches the global minimum. One solution to this problem has been developed by Binsch[21] and also used by Hägele.[22] These authors use a generalization of the least-squares formalism to "flatten" the $?^2$ function and so remove the local minima. This strategy helps convergence to a reasonable solution even from poor starting values. However, the "flattening" prevents accurate determination of parameters. Therefore, once a solution has been found, the flattening is decreased in stages, allowing progressively more accurate determination of the parameters while staying near the global minimum. The final stage, with no flattening at all, is a true least-squares fit. To use this kind of iteration, the user must supply experimental spectra, the spin system, and some reasonable starting values for the shifts and coupling constants, but does not have to do any peak assignments.

A related approach has been implemented by Laatikainen. He uses an integral transformation to introduce an artificial broadening of the spectrum in the initial stages of the fitting procedure; this broadening is then reduced in several stages. In the final refinement stages, this may then be followed by a standard assignment iteration.[23]

8.2. Pros and cons of full-lineshape iteration

One of the main advantages of full-lineshape analysis is that you can use it to optimize *any* parameter that affects the appearance of the spectrum: not just shifts and coupling constants, but also linewidths and rate constants. You can even "fit away" imperfections in the spectrum like baseline and phasing errors.

A drawback of the method is that it is very sensitive to the quality of the observed spectrum. Small amounts of impurities, the presence of "humps" in the baseline, intensity distortions or incorrect phasing may trip up the fitting process and prevent you from finding an acceptable solution. Therefore, you should always try to obtain the best possible spectrum if you plan to do a full-lineshape iteration, and pay careful attention to phasing. Even so, it may be necessary to do some "editing" of the experimental spectrum before you start the full-lineshape iteration.

8.3. Strategy

The analysis of an NMR spectrum is usually undertaken to extract a set of parameters (shifts and coupling constants). There are three distinct phases in this process:

? Arriving at a set of parameters.

? Refining the parameters.

? Checking for correctness and/or uniqueness.

Full-lineshape least-squares analysis uses a least-squares procedure to obtain the best fit between the observed and calculated spectrum. One of the most attractive features of this method is that the precise numerical values of the final parameters do not depend on the way you arrive at them (within limits; there may be several distinct, acceptable solutions). Thus, it is allowable to use any

number of tricks to arrive at a "reasonable" set of parameters, as long as you use a complete least-squares fit to the actual observed spectrum to obtain your final refined values. We will discuss the three phases of the process (finding a solution, refining it, and checking for alternatives) separately in the following sections.

8.4. Finding a solution

The chances of obtaining a reasonable solution from a full-lineshape iteration depend critically on the quality of the experimental spectrum. A "wavy" baseline, impurity peaks or incorrect relative intensities will send the procedure way off in its initial phase, and it will probably never get back on track. So start with a good, well-phased spectrum. Use available tricks of your spectrum processing software to get a good baseline. Displaying the integral can be very helpful here, since errors in the baseline show up as non-constant integrals in regions not containing any peaks. If your processing program allows it, you may also want to remove impurity peaks and noisy areas not containing any peaks from the spectrum. After you are satisfied with this manipulated spectrum, save it and set up the iteration. If you are fitting only a single multiplet, you can do the iteration in a single "window". If there are large empty areas between the parts of the spectrum you are interested in, it is usually better to define several windows, one for each "occupied" part of the spectrum. In this way, you will get a higher accuracy and avoid useless fitting to baseline noise.

If, despite the above precautions, the procedure does not converge to a meaningful solution, you can restart it with a different set of parameters. You can also let the program itself generate more or less random start values for coupling constants: in that way, you can do a large series of trials overnight, and inspect the resulting solutions one by one in the morning. If your initial guess looked reasonable, but the full-lineshape iteration seems to make it worse, you could try starting with less "flattening", which tends to keep you closer to the start values (of course, it may also prevent you from finding the correct solution). Do not break off an iteration too soon: it will almost always drift away in the first few cycles, but often come back later on.

The above guidelines - especially the part about removing impurities and baseline noise - may look like "cheating". Remember, however, that we are only trying to *find* a solution at this stage. Once this has been done, it is time to do a definitive refinement without any cheating.

8.5. The final refinement

Objectively, the only "correct" way of refining parameters is a direct least-squares fit of observed to calculated spectrum, without any "fudging" (except phasing and baseline correction). You should always finish your lineshape analysis by doing such a refinement, because this is the only way to obtain a meaningful set of error limits. To do this, take the solution obtained in the last section, but set up a new iteration, this time using the raw observed spectrum. Set the "flattening" parameter to zero to do a normal least-squares fit, and start the iteration. Even in the presence of impurities and baseline errors, this fit will seldom run wild: it will remain "trapped" in its current local minimum. If the iteration has converged, save the data and print the error analysis. Use these results for any illustration you plan to create, not the ones showing "edited" experimental spectra.

8.6. Checking your solution

Once you have obtained reasonable-looking fit results, either by assignment or full-lineshape iteration, you might sit back and think you have solved the problem. However, your reasonable-looking solution may still not be the right one. There may be other combinations of parameters that give rise to exactly the same calculated spectrum and are therefore also candidates; there may even be solutions that give a better fit to the observed spectrum. So, it is important to ask whether you have *a* solution or *the* solution.

Unfortunately, there is no general way to answer this question. There are a number of possible sources of error in any solution you obtain:

? You may have chosen the wrong spin system. In that case, any parameters you have obtained via a fitting procedure will probably be meaningless, since they have nothing to do with the parameters of the actual system. If your fit looks good, the chances of this kind of error are rather small. However, there are examples of AA'XX' and AA'A"A'"XX' systems giving very similar spectra for the A-nucleus. In general, you should be careful if you are fitting the spectrum for a single nucleus (e.g. ^{31}P) in a system containing several NMR-active nuclei (e.g. ^{31}P and ^{103}Rh).

? Some parameters (or combinations of parameters) may not affect the spectrum at all, and can therefore not be determined by iteration. Fitting will still give you a value for these, but the value will be meaningless. Careful inspection of the error analysis (see next section) can alert you to such situations.

? The spectrum may not contain enough detail for a complete determination of all parameters. For example, if the linewidth of the observed spectrum is 2 Hz, coupling constants cannot be determined to a much greater accuracy than this. This can be especially important in rate processes (chapter 6).

There may be several solutions giving very similar spectra. Often, these alternatives differ only in the signs of one or more coupling constants. It is important that you try to find out whether such alternatives really exist. If there are only a few independent coupling constants in the system, you can easily try out all combinations by hand. If there are more, your simulation program may be able to test them in a systematic fashion. The alternative solutions may give rise to slightly different spectra, in which case you may be able to judge from the quality of the fit which solution is the most likely one. Often, however, there are different sign combinations that produce exactly the same spectrum. In that case, you can only try to rule out some possibilities on the basis of "general knowledge" (see section 2.7). If you are not completely sure, it is often better to report several possibilities.

9. Error analysis

Once you have finished your iterative simulation, you will probably want to report the results. There are standard ways to report results of least-squares fits; we will discuss a gNMR error-analysis as an example, but other programs will produce very similar output.

In a least-squares analysis, it is important that variables are scaled, so that similar variations in different parameters have similar effects. The scaling does not have to be perfect, but differences in "parameter sensitivity" in the order of 10^6 will wreak havoc in most least-squares fits. If the program does scaling, the scaling factors for the different parameters will be printed somewhere.

The variance-covariance matrix is a square, symmetric matrix: the rows and columns are numbered for the parameters. The variance-covariance matrix shows parameter variances (squares of the estimated standard deviation, e.s.d. or ?) on its diagonal, and covariances as off-diagonal elements. The matrix may be expressed in either scaled or unscaled parameters; be sure to check on this before using the results. gNMR uses unscaled values; the matrix elements are in more or less "arbitrary units" related to spectrum amplitudes, so it is hard to use the values directly. The main reason to look at this matrix is that large covariances imply strong dependencies between parameters, and indicate that it may be dangerous to cite the single-parameter ?'s as independent error limits. Covariances can be either positive or negative, but variances are always positive (because they are squares).

```
Variance-Covariance Matrix
```

	1	2	3	4	5	6	7
1	1.96e+03	-5.74e+02	1.70e+04	4.92e+03	-5.78e+03	6.08e+03	3.03e+02
2	-5.74e+02	1.97e+03	-1.71e+04	-4.95e+03	5.82e+03	-5.04e+03	-5.45e+02
3	1.70e+04	-1.71e+04	5.03e+06	8.40e+05	-8.54e+05	7.69e+05	5.64e+04
4	4.92e+03	-4.95e+03	8.40e+05	1.55e+05	-1.52e+05	1.15e+05	9.27e+03
5	-5.78e+03	5.82e+03	-8.54e+05	-1.52e+05	1.63e+05	-1.45e+05	-1.12e+04
6	6.08e+03	-5.04e+03	7.69e+05	1.15e+05	-1.45e+05	1.98e+06	5.27e+04
7	3.03e+02	-5.45e+02	5.64e+04	9.27e+03	-1.12e+04	5.27e+04	8.10e+03

The most important part of the error analysis, and also the part that is least looked at (and not even printed by some programs) is the singular value (SV) analysis. This can show you how well the parameters you tried to optimize are determined by the experimental data. The SV analysis is printed as a square matrix (see below). The columns are headed by the "singular values", and the rows are labeled by the (scaled) parameters. There are usually some minor or major dependencies between the parameters you try to optimize; the SV analysis transforms your set of parameters into an "orthogonal" set of linear combinations that represent independent search directions. Each column shows one such linear combination; the numbers above each column are a measure of the precision with which the movement in that particular direction is determined (the larger, the better). If all singular values are comparable in magnitude (say, to within a factor of 1000), your parameters are apparently all well-determined by the data. In the example shown below, parameters 3 and 6 are clearly less well-determined than the others, but this is still a reasonable fit. Sometimes, you may find that the sum of two (or more) parameters is ill-determined, while their difference is well-determined by the data. In such cases, you may not see any unusually large single-parameter errors, but you still have a problem with your data.

```
Singular value decomposition
```

	2.745e-02	2.689e-02	1.301e-02	1.162e-02	6.283e-03	7.454e-04	4.265e-04
1	-0.700924	0.694324	-0.066754	-0.025402	-0.146648	0.001076	0.003488
2	0.677230	0.718661	0.019420	0.051291	0.147873	-0.000497	-0.003472
3	-0.042703	-0.000720	-0.006720	-0.018661	0.227982	-0.213682	0.948761
4	0.072605	0.002961	0.392880	0.653450	-0.621584	-0.043293	0.158518
5	-0.207035	-0.000554	0.387279	0.514359	0.717885	0.028812	-0.162473
6	0.001330	-0.001246	-0.013783	0.021987	0.002583	0.975278	0.219428
7	-0.010295	0.037812	0.831019	-0.551662	-0.054039	0.021585	0.012448

Occasionally, a certain linear combination of parameters is not determined at all by the data. This may happen, for example, when a certain shift or coupling constant does not affect the appearance of the spectrum. You will then see a zero singular value in the SV matrix. Take care! The corresponding direction has had to be excluded from the calculation of the normal variance-covariance matrix, because including it would mean dividing by zero. So, you may see a small (or even zero) estimated standard deviation for such an undetermined parameter. The moral: **please read the singular-value analysis**!

10. 1-D NMR data processing

10.1. Introduction

The main focus of this booklet is on using simulation to analyze NMR spectra. Before doing this, however, you need to have an NMR spectrum. Moreover, it has to be of sufficient quality to let you do the desired analysis.

It is impossible to do justice to the topic of recording and processing NMR spectra in the space of a few pages. Many books have been written on the subject; for a recent one that gives an excellent overview of established and new techniques, see ref. 24. Nevertheless, it might be useful to go through some of the most important steps of the process here.

10.2. Recording the spectrum

If you are planning to do a full-lineshape iteration, you need a good field homogeneity. Ill-adjusted high-order shims usually cause peaks to have broad "feet". The spectrum will still look good enough to the eye, but the intensity hidden in the baseline is likely to throw the iteration off the track, especially if the "feet" are asymmetrical. Such "feet" are less of a problem for assignment iteration, where the primary concern is high resolution near the tops of peaks.

Make sure you use enough data points when recording a spectrum. In these days of cheap storage media, there is no good reason to record 8K or 16K 1-D NMR spectra. Resolution lost at this stage can never be fully recovered.

Several brands of NMR machines now use digital filtering techniques by default. There is nothing against this, and the resulting spectra may be of significantly higher quality. However, some machines store and process FID's still containing filter functions. This is not a problem as long as the file stays on the NMR machine, but if you try to export it to other processing software that software may not be able to handle the filtered FID. If you have to use custom filtering, we recommend you remove the filter (sometimes called "converting the FID to analog form", which is a misnomer) before exporting the data.

10.3. Standard processing

Normally, an FID is multiplied with one or more weighting functions, Fourier transformed, and phased. The optimal choice of weighting function depends on the intended use of the spectrum. For full-lineshape iteration, you want to have peaks without broad feet, and a good signal-to-noise ratio. This is best achieved by a Gaussian multiplication function. For assignment iteration, sharp peaks are important, but some noise is tolerable, as long as you can distinguish between real peaks and noise or "spikes" by eye. An unweighted FT or modest resolution enhancement may be best here.

Zero-filling by a factor of 2 may be useful, but anything beyond that is merely cosmetic and will not produce better iteration results.

Correct phasing is extremely important for full-lineshape iteration. The reason for this is that the imaginary (or dispersion) component is much broader and has a much larger area than the real (or absorption) component. If the automatic phasing function of your NMR software is any good, we recommend that you use it for all spectra intended for full-lineshape iteration (it may be a good idea to do a rough phasing by hand first). The quality of the phasing is easily judged from the spectrum integral: it should not *dip* immediately before or after peaks. Phasing is somewhat less of an issue for assignment iteration, although phasing errors above ?20° may introduce significant and systematic errors in peak positions.

10.4. Custom processing

Most processing software allows you to do a lot of special processing. At the very least, there will be options for baseline correction. This is important for full-lineshape iteration, as mentioned earlier. The quality of the baseline is easily judged from the integral, which should be strictly horizontal in regions not containing any peaks.

Be very careful with baseline corrections in chemical-exchange spectra. These spectra usually have broad lines, and it is easy to correct away the feet of such lines, resulting in poor matches between experimental and simulated spectra. In such cases, it may be useful to add an innocent compound having peaks outside of the region of interest, and to use these (sharp) peaks for phasing and baseline correction.

Custom processing may also include various smoothing techniques, options to remove parts of the spectrum containing impurities, etc. While such tricks can be useful at times, one should not normally use them to generate spectra for presentations: that is simply too close to cheating. However, using *cooked* spectra to help along the initial stages of an iteration is perfectly legitimate, as discussed in section 8.4.

10.5. Linear prediction and other processing techniques.

Apart from the standard Fourier transformation, there are a few other techniques for generating a spectrum from an FID. The most important of these are *linear prediction* and *maximum entropy*.

Linear prediction effectively does a direct fit of a set of decaying sinusoids to the FID. There are several variations of this method. Some are merely designed to improve the quality of the transformed spectrum by throwing away noise components, while others generate a list of peaks directly, without even going through a transformed spectrum. Linear prediction is more computationally intensive than FFT, but the difference is not prohibitive, and we believe the technique will become more important in the future.

Maximum entropy is a statistical method of generating a transformed spectrum from an FID, which achieves a better S/N than standard FFT. This is also computationally expensive, and moreover there are too many parameters that can be varied and not enough experience to let this play an important role in routine spectrum processing at the moment. An important disadvantage in the current context is that it is nonlinear, which makes it less suitable for use in combination with full-lineshape iteration.

A. Examples of typical second-order systems

The appearance of second-order spectra can be complicated. and often bears no obvious relation to the original spectral parameters. This makes setting up the initial simulation difficult, since you don't know where to start. Once you recognize the pattern of a multiplet and can reproduce this in a simulation, obtaining more accurate parameter values by e.g. iteration is easy.

The examples in this chapter are intended to help you recognize such patterns. In each section, you will see spectra calculated for a particular type of system (A_2B_3, AA'BB', AA'X) and several sets of parameter values (shifts and couplings). The parameters have been chosen to illustrate typical spectrum patterns and do not necessarily represent realistic values. All spectra have been calculated for a spectrometer (^1H) frequency of 100 MHz. The filenames mentioned with the examples refer to sample files distributed with gNMR.

In general, it is impossible to deduce the absolute signs of coupling constants from NMR spectra. In many cases, however, relative signs may affect the spectrum appearance. Therefore, you will see examples of both positive and negative coupling constants in the examples below. Changing the signs of all coupling constants simultaneously will never change the spectrum appearance, but changing the sign of only one coupling may have a large effect.

A.1. The A_nB_m systems

The appearance of these spectra is completely determined by a single parameter, the ratio J/? ?. Figures 19 and 20 show these spectra for values of 0.1, 0.3, 1.0 and 3.0 of this ratio.

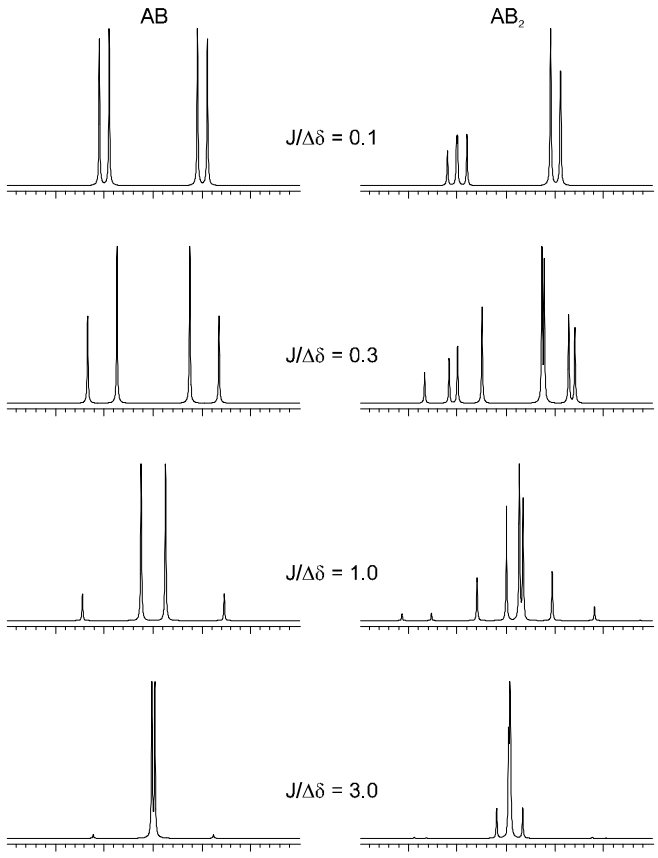


Figure 19. AB and AB_2 spectra.

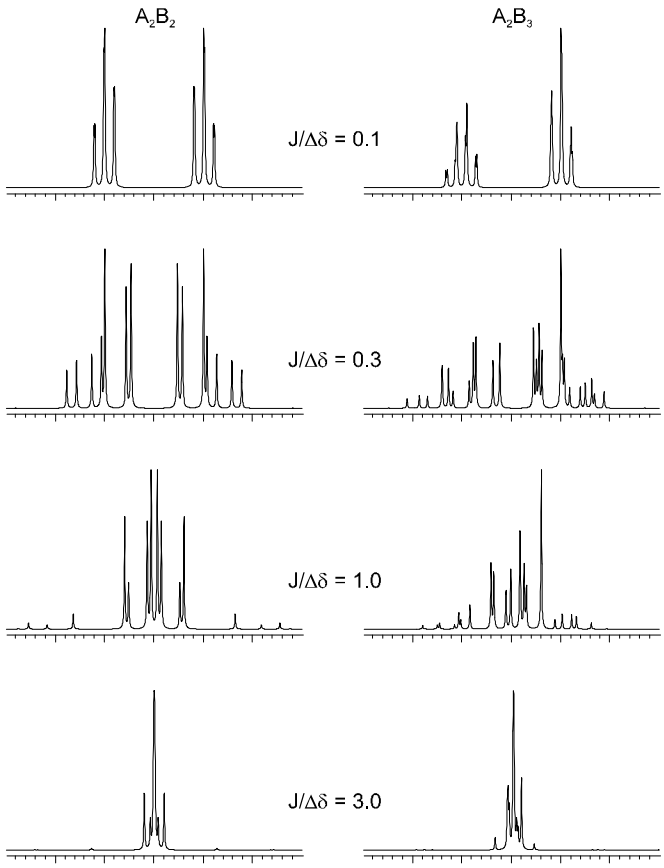
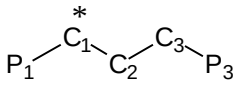


Figure 20. A_2B_2 and A_2B_3 spectra.

A.2. The AA'X system

This consists of two nuclei with (nearly) identical chemical shifts (A and A') coupling to a third with a very different shift (X). J_{AX} and $J_{A'X}$ are different (if they were not, this would be an A_2X system).

Systems of this type are often encountered as a consequence of the presence of isotopes. For example, the C_1 resonance of 1,3-diphosphinopropane is the X-part of an AA'X system. The presence of the ^{13}C nucleus induces a small isotope shift ? ? for P_1, and J_{P1C} ? J_{P2C}.

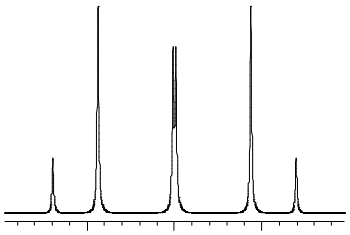


The X-part of an AA'X-system is always symmetric. It consists of two lines of intensity 0.25, and an set of four lines with total intensity 0.5. There are five independent parameters that influence the spectrum appearance (J_{AX}, $J_{A'X}$, $J_{AA'}$, $?_X$ and $? ?_{AA'}$) and only four independent peak positions, so you will need to use intensity data to determine all parameters. Sometimes, you may already know the value of one of the parameters (e.g., $J_{A'X} = 0$) in which case the other four parameters can be determined from peak positions alone. The low-intensity pair of "combinations lines", which are essential for the determination of $J_{AA'}$, frequently have a larger linewidth than the other lines, which can make them hard to see.

The sign of $J_{AA'}$ does not affect the spectrum. The relative signs of J_{AX} and $J_{A'X}$ are important, but changing *both* will leave the spectrum unchanged. In the limit of large $J_{AA'}$, the spectrum looks like an A_2X system (AA'X_2: "virtual triplet"; the A atoms become effectively equivalent). In the limit of large ? ?, it becomes an AMX spectrum (AA'X_7: doublet of doublets).

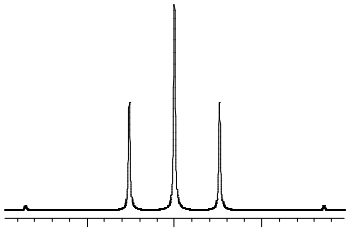
AA'X_1

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.010	20.00	
3	31P	0.000	2.00	15.00



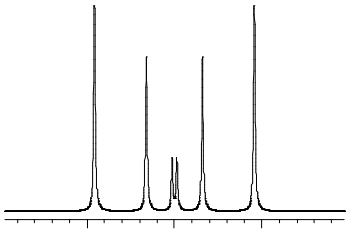
AA'X_2

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.000	11.00	
3	31P	0.000	2.00	21.00



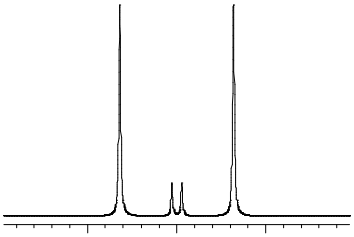
AA'X_3

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.010	15.00	
3	31P	0.000	8.00	2.00



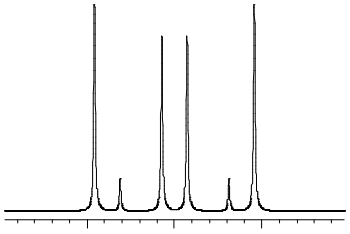
AA'X_4

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.020	15.00	
3	31P	0.000	1.00	4.00



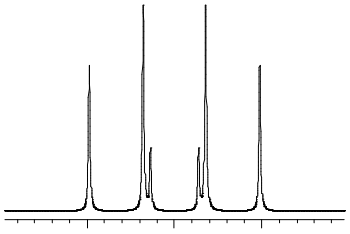
AA'X_5

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.100	15.00	
3	31P	0.000	8.00	6.00



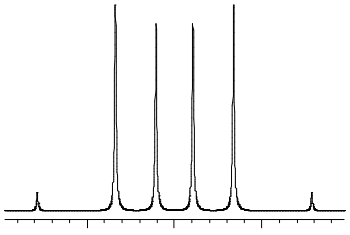
AA'X_6

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.100	15.00	
3	31P	0.000	-6.00	6.00



AA'X_7

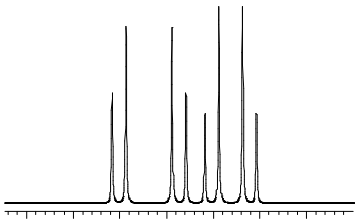
		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	13C	0.000		
2	31P	0.200	15.00	
3	31P	0.000	2.00	17.00



The AA' part of an AA'X spectrum always consists of two AB "quartets", with the same coupling constant $J_{AA'}$ but different apparent shifts; none of the other four relevant parameters ($?_A$, $?_{A'}$, J_{AX}, $J_{A'X}$) can be extracted directly from peak positions in the spectrum. If the chemical-shift difference $??_{AA'}$ is large, it may be difficult to determine which left half of one AB belongs to which right half: the peak positions will be the same, only the intensities are different. Even if this choice has been made correctly, there are always two possible solutions giving rise to identical spectra (this corresponds to switching left and right halves of one of the AB quartets). Determining which solution is correct requires either measurement of the X-part of the spectrum or re-recording the AA' part at a different spectrometer frequency. The examples below illustrate the two independent solutions for one spectrum (`AA'X_11`, `AA'X_12`), solutions for two alternative choices of the AB halves (`AA'X_13`, `AA'X_14`), an example where the AB halves are all interspersed (`AA'X_15`) and one in which one of the AB quartets has an effective chemical shift difference close to zero (`AA'X_16`). As for the X-part, only the relative signs of J_{AX} and $J_{A'X}$ are important, and the sign of $J_{AA'}$ does not affect the spectrum.

`AA'X_11`

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	1H	0.000		
2	1H	0.100	-3.00	
3	31P	0.000	15.00	20.00

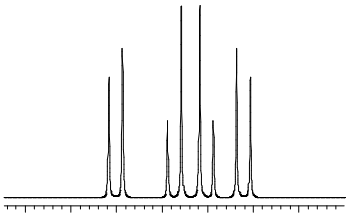


`AA'X_12`

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	1H	0.037		
2	1H	0.063	-3.00	
3	31P	0.000	7.46	27.54

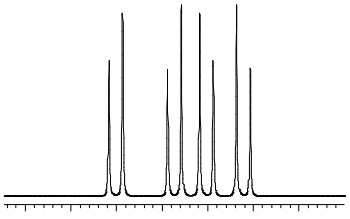
`AA'X_13`

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	1H	0.135		
2	1H	-0.035	-3.00	
3	31P	0.000	-13.15	8.35



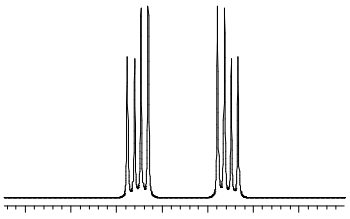
`AA'X_14`

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	1H	-0.036		
2	1H	0.136	-3.00	
3	31P	0.000	8.05	12.91



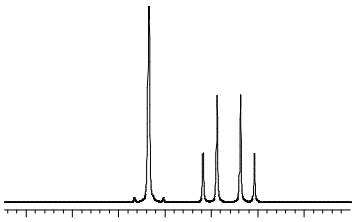
`AA'X_15`

		?	J (Hz)	
	Nucleus	(ppm)	1	2
1	1H	0.047		
2	1H	0.063	-3.00	
3	31P	0.000	-19.46	19.54



AA'X_16

	Nucleus	? (ppm)	J (Hz) 1	2
1	1H	0.027		
2	1H	0.070	-3.00	
3	31P	0.000	20.44	14.06

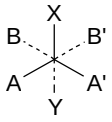


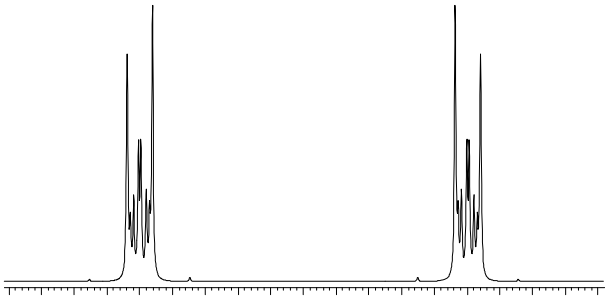
A.3. The AA'BB' system

Six independent parameters ($?_A$, $?_B$, $J_{AA'}$, $J_{BB'}$, J_{AB} and $J_{A'B}$) determine the appearance of this type of spectrum. Therefore, there are many possible patterns. Here, we just illustrate a few of the most common ones: ethylene groups with hindered or free rotation, coordinated ethylene, and *o*- and *p*-substituted benzene. When analyzing these spectra, it is important to realize that one cannot distinguish between $J_{AA'}$ and $J_{BB'}$, or between J_{AB} and $J_{A'B}$, on the basis of the spectra alone. The relative signs of J_{AB} and $J_{A'B}$ are important, but changing the signs of $J_{AA'}$ and $J_{BB'}$ usually has only a small effect on the spectrum.

anti- staggered constrained X-CH_2-CH_2-Y (AA'BB'_1)

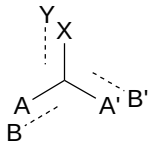
	Nucleus	? (ppm)	J (Hz) 1	2	3
1	1H	1.000			
2	1H	1.000	-14.00		
3	1H	3.000	3.00	12.50	
4	1H	3.000	12.50	3.00	-16.00

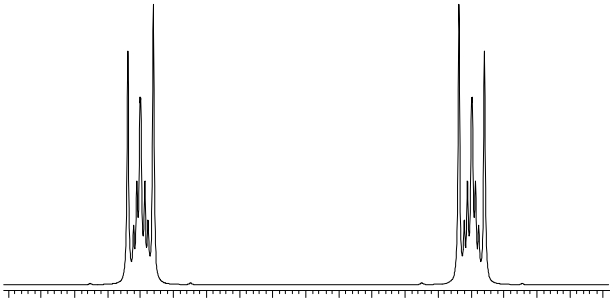




syn-eclipsed constrained X-CH_2-CH_2-Y (AA'BB'_2)

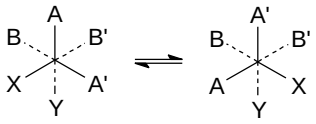
	Nucleus	? (ppm)	J (Hz) 1	2	3
1	1H	1.000			
2	1H	1.000	-14.00		
3	1H	3.000	11.00	4.50	
4	1H	3.000	4.50	11.00	-16.00

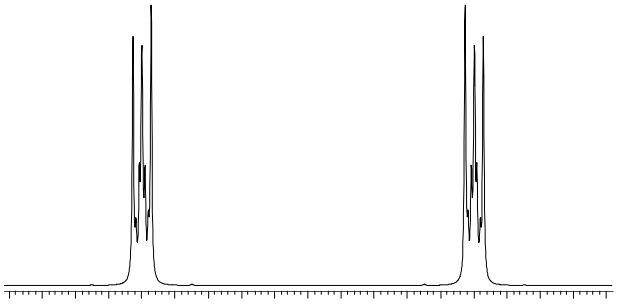




gauche-staggered constrained X-CH_2-CH_2-Y (AA'BB'_3)

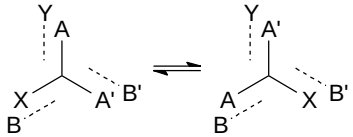
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	1.000			
2	1H	1.000	-14.00		
3	1H	3.000	3.00	8.00	
4	1H	3.000	8.00	3.00	-16.00

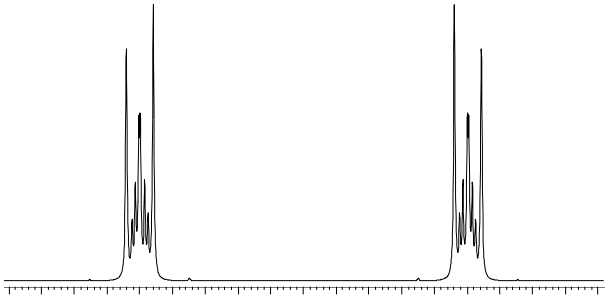




gauche-eclipsed constrained X-CH_2-CH_2-Y (AA'BB'_4)

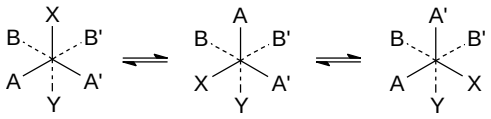
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	1.000			
2	1H	1.000	-14.00		
3	1H	3.000	4.50	12.00	
4	1H	3.000	12.00	4.50	-16.00

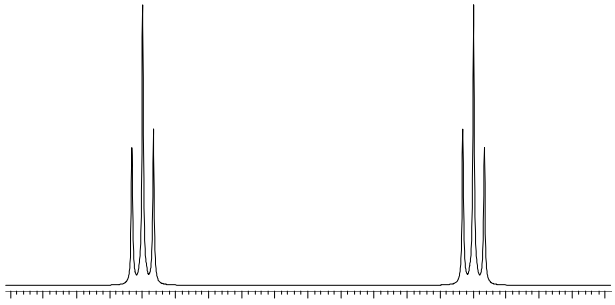




rotation-averaged unconstrained X-CH_2-CH_2-Y (AA'BB'_5)

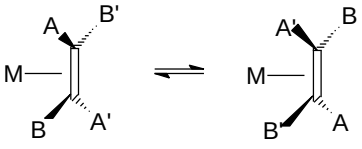
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	1.000			
2	1H	1.000	-14.00		
3	1H	3.000	6.00	7.00	
4	1H	3.000	7.00	6.00	-16.00

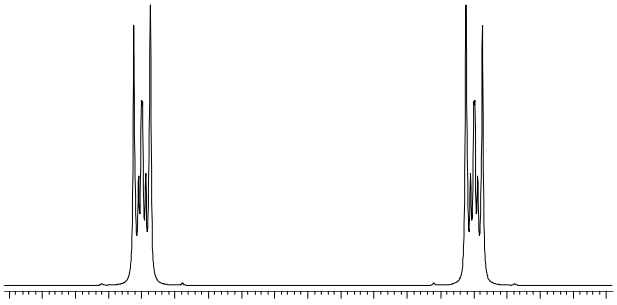




Freely rotating coordinated ethylene (AA'BB'_6)

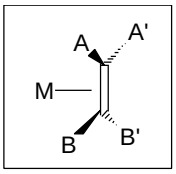
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	1.000			
2	1H	1.000	13.00		
3	1H	3.000	2.00	8.00	
4	1H	3.000	8.00	2.00	11.00

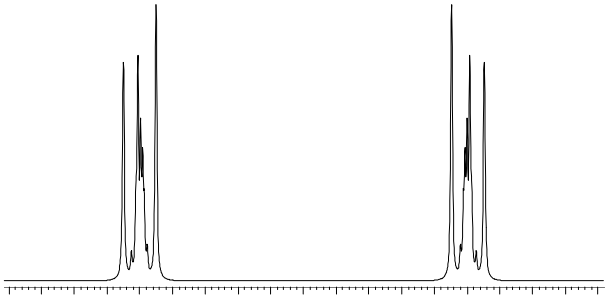




Static coordinated ethylene with mirror plane through C-C bond (AA'BB'_7)

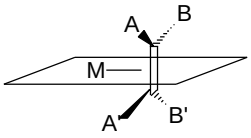
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	1.000			
2	1H	1.000	1.50		
3	1H	3.000	8.00	12.00	
4	1H	3.000	12.00	8.00	2.50

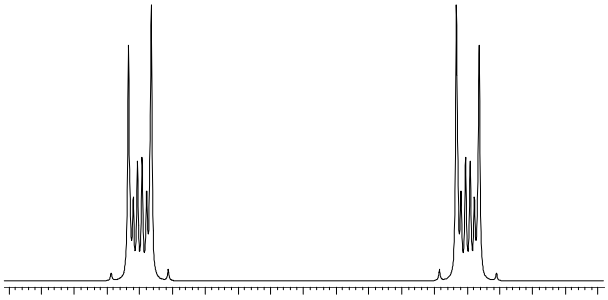




Static coordinated ethylene with mirror plane bisecting C-C bond (AA'BB'_8)

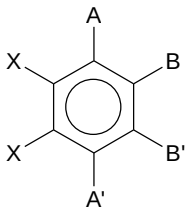
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	1.000			
2	1H	1.000	7.00		
3	1H	3.000	2.00	12.00	
4	1H	3.000	12.00	2.00	9.00

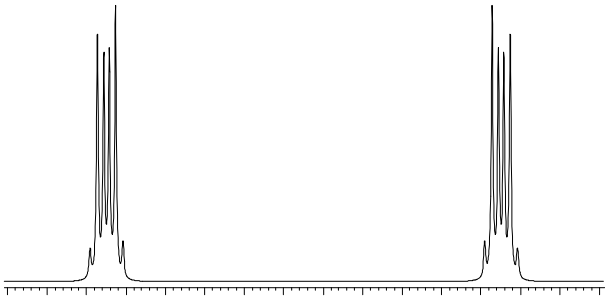




o-Disubstituted benzene (AA'BB'_9)

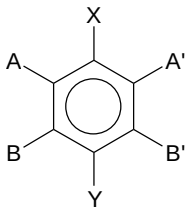
		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	6.500			
2	1H	6.500	0.25		
3	1H	8.500	8.00	1.20	
4	1H	8.500	1.20	8.00	7.00

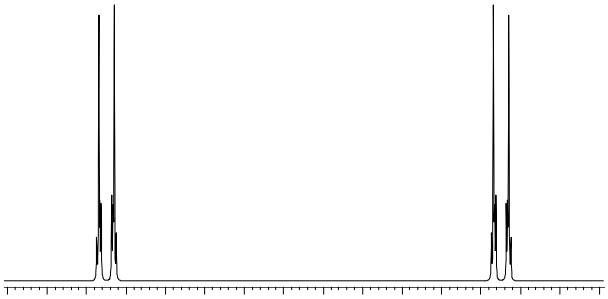




p-Disubstituted benzene (AA'BB'_10)

		?	J (Hz)		
	Nucleus	(ppm)	1	2	3
1	1H	6.500			
2	1H	6.500	1.50		
3	1H	8.500	7.50	0.25	
4	1H	8.500	0.25	7.50	0.80





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